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CONTENTS

IMAGERY OF THE ANEURYSM OF GALEN VEIN

Alexandru Cărăuleanu[1], Răzvan Socolov[1], Ciprian Ilea[1], Maria Stamatin[2], Demetra Socolov[1]

Abstract

The aneurysm of Galen vein is a rare anomaly of intracranial circulation. Galen vein malformations prognosis in children is unfavorable. Antenatal, Galen vein aneurysm is suspected when an ultrasound examination identifies in the brain, a liquidian structure localized behind the third ventricle. Color Doppler ultrasound helps in differentiating aneurysm of Galen vein from other cystic cerebral median lesions. Ultrasound diagnosis of these malformations could facilitate postnatal therapy, greatly improving prognosis.

Key words: Galen vein, aneurysm, ultrasound

Introduction

The aneurysm of Galen vein is a rare anomaly of intracranial circulation, representing 1% of the intracranial circulation malformations, but it represents also 30% of all fetal vascular malformations.(1) It occurs as a result of direct communication between arterial and venous pros encephalic median network. Raybaud et al.(2) found that this abnormal development occurs between 6 and 11 weeks of intrauterine life. Although this anomaly appears in this early period of gestation, prenatal diagnosis is usually possible only in the third trimester, but most cases were postnatally diagnosed. Galen vein malformations prognosis in children is unfavorable, with a high risk of postnatal mortality and a 50% increased risk of neurological disabilities (3). Antenatally, Galen vein aneurysm is suspected when an ultrasound antenatal examination identifies in the brain a structure localized behind the third ventricle. Color Doppler ultrasound helps in differentiating aneurysm of Galen vein from other cystic cerebral median lesions. Ultrasound can also diagnose associated complications such as hydrocephaly or heart failure. The aneurysm of Galen vein can lead to cardiac failure due to the size of the arterio-venous shunt that can steal more than 80% of the cardiac input, with large amount of blood under high pressure returning to the right heart and pulmonary circulation, this is the most common cause of death in these patients.(4) Compression by the dilated vessel of the drainage holes from the cerebrospinal fluid circuit (Monro and Magendie) may induce hydrocephaly, another complication of this condition. If a patient presents congestive heart failure and other cardiac causes have been excluded, we should consider also, the possibility of an aneurysm of Galen vein.(5)

Case presentation

A pregnant woman, primigesta, nulipara, of 27 years old, with no significant pathological personal history, was monitored by the obstetrician from 2 months of pregnancy. Previous ultrasounds showed an apparently normal fetus without structural abnormalities and normal development. The ultrasound performed at 34 weeks of pregnancy, showed at the level of the brain, in the midline, an oval fluid structure of about 5/3 cm placed behind the third ventricle and above the thalamus. The other intracranial components were normal, including third and fourth ventricles. Color Doppler ultrasound identified a turbulent blood flow with a speed of 35 to 40 cm / sec. Hence, the suspicion of arterio-venous aneurysm at the level of the Galen vein vas formulated. (fig. 1,2,3,4).

The possibility of a cardiomegaly with tricuspid insufficiency was also taken into account. At the ultrasound examination of the heart, a right ventricle hypertrophy and a dilated pulmonary artery was observed. Problems of diagnosis, prognosis and therapeutic possibilities were discussed with an interdisciplinary team including an obstetrician, a sonographist, a neurosurgeon, a neonatologist and with the parents, of course. A caesarean section was performed at 37 weeks of pregnancy , resulting a new born alive,of 48 cm length, head circumference of 33 cm, chest circumference of 31 cm, Apgar = 8. Immediately postpartum, the newborn showed relatively good general condition, with acrocyanosis, the auscultation describes a systolic murmur grade II/VI localised in left parasternal position, subcostal discrete retraction, but with a saturation and a normal pulse. Following clinical examination and paraclinical tests in particular, the antenatal ultrasound performed at 34 weeks of amenorrhea the diagnosis of Galen vein aneurysm was formulated. The newborn was transferred in the neonatal intensive care unit. The transfontanelar ultrasound showed a venous vascular, central cerebral inter-talamic image, confirmed to be a Galen vein aneurysm (fig. 5).

Echocardiography performed after birth describes the following: large, permeable foramen ovale, permeable ductus arteriosus with left-right shunt, increased dilation of coronary sinus, pulmonary hypertension with right heart dilatation, pulmonary artery dilatation and tricuspid reflux, normal systolic function and ventricular contractility disorders (fig. 6,7).

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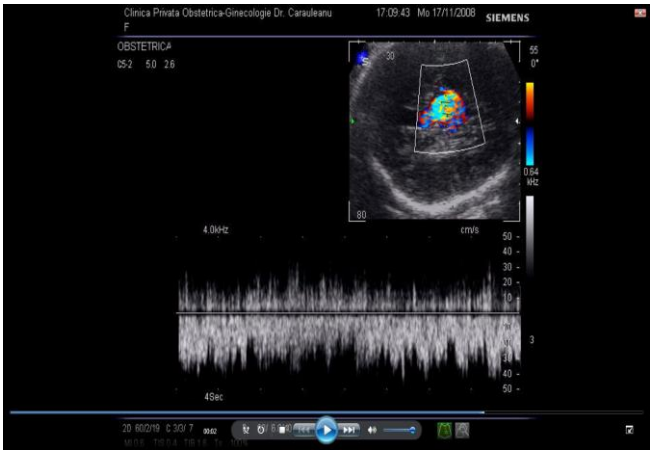

Figure 1. Pulsed Doppler image in the aneurysm.

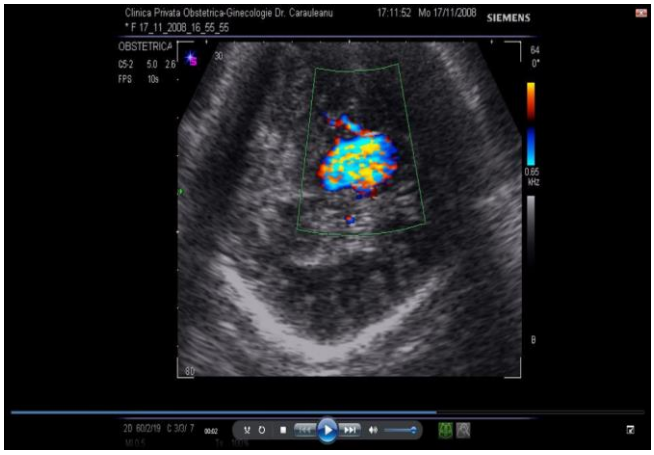

Figure 2. Color Doppler image in the aneurysm.

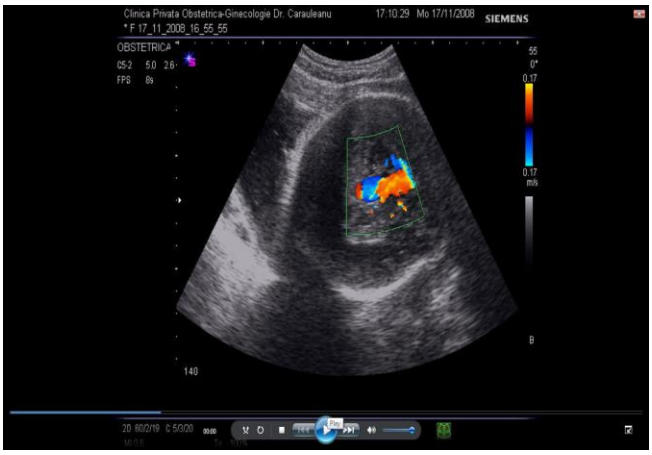

Figure 3. Color Doppler image in the aneurysm.

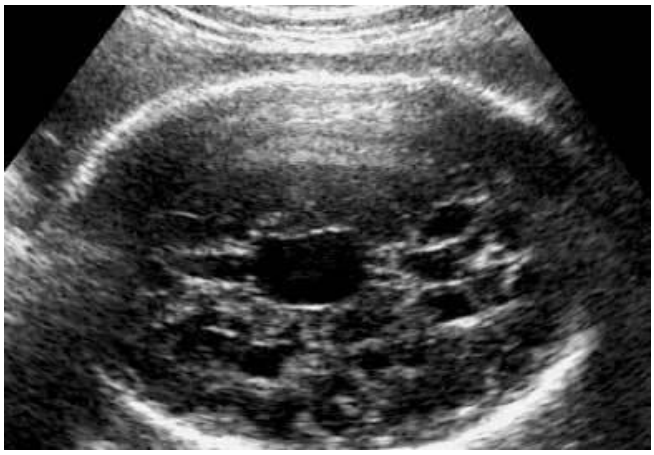

Figure 4. 2D ultrasound image in the aneurysm.

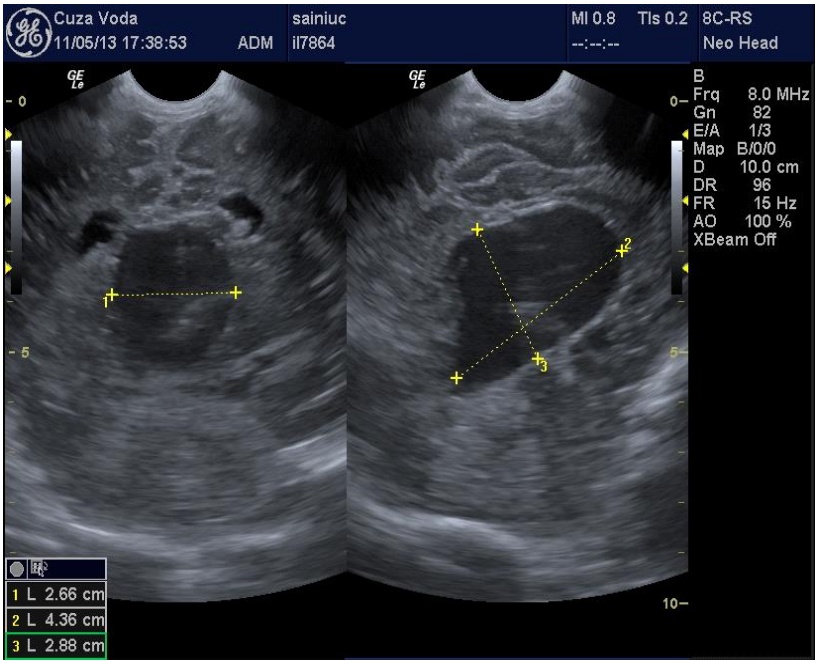

Figure 5. Transfontanelar 2D ultrasound in the newborn.

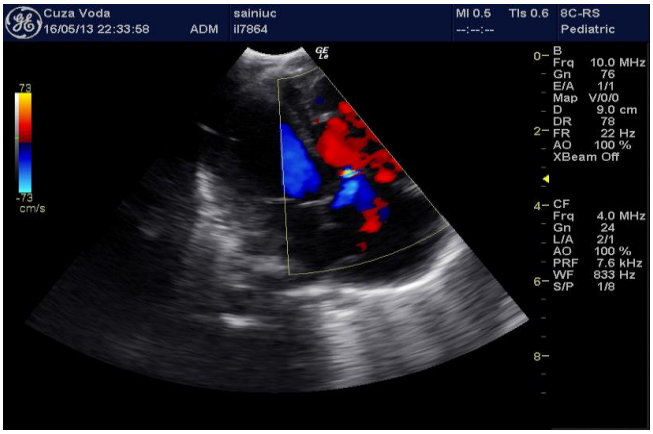

Figure 6. Doppler echocardiography in the newborn.

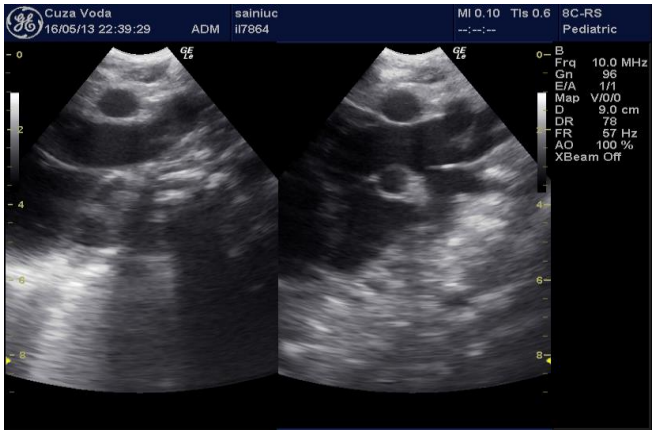

Figure 7. Echocardiography in the newborn.

To confirm the diagnosis of Galen vein aneurysm, a CT with contrast is performed showing a giant aneurysmal dilatation of a Galen vein with dimensions of 5,1/2,97/3,5 cm, with homogeneous filling,with nutrient vessels derived from pericalosal artery, polygon of Willis, temporal enlarged fluid spaces, spaced lateral ventricles (fig. 8,9).

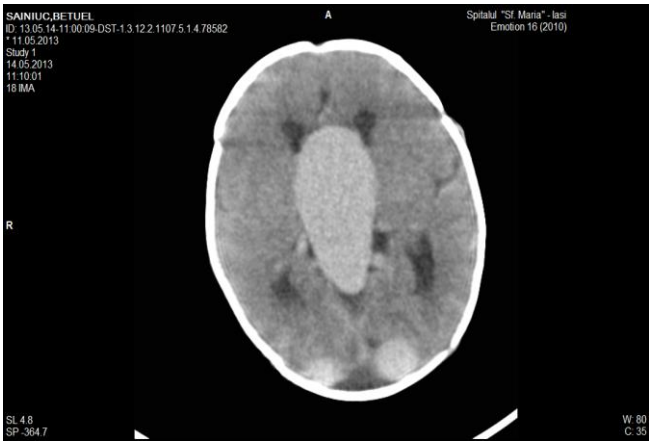

Figure 8. Cerebral CT without contrast - Galen vein aneurysm (day 3).

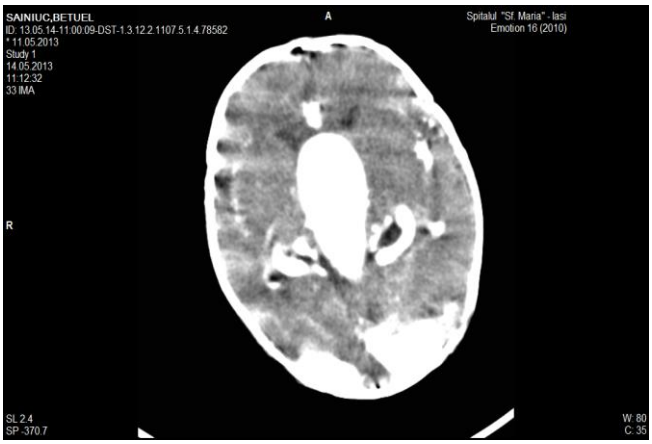

Figure 9. Cerebral CT with contrast - Aneurysm of Galen vein.

During the 2-nd/3-rd day after birth, the newborn's condition deteriorates, on day 5 his condition is mediocre with rapidly progressive edemas, progressive heart failure, hepatomegaly, so that, on day 9, the condition worsen, resulting in newborn death by irreversible cardiac arrest, resistant to resuscitation. The necropsy found a Galen vein aneurysm complicated with subdural posterior hemorrhage (fig. 10), heart failure, pulmonary multifocal hemorrhage, liver, kidney and spleen with stasis.

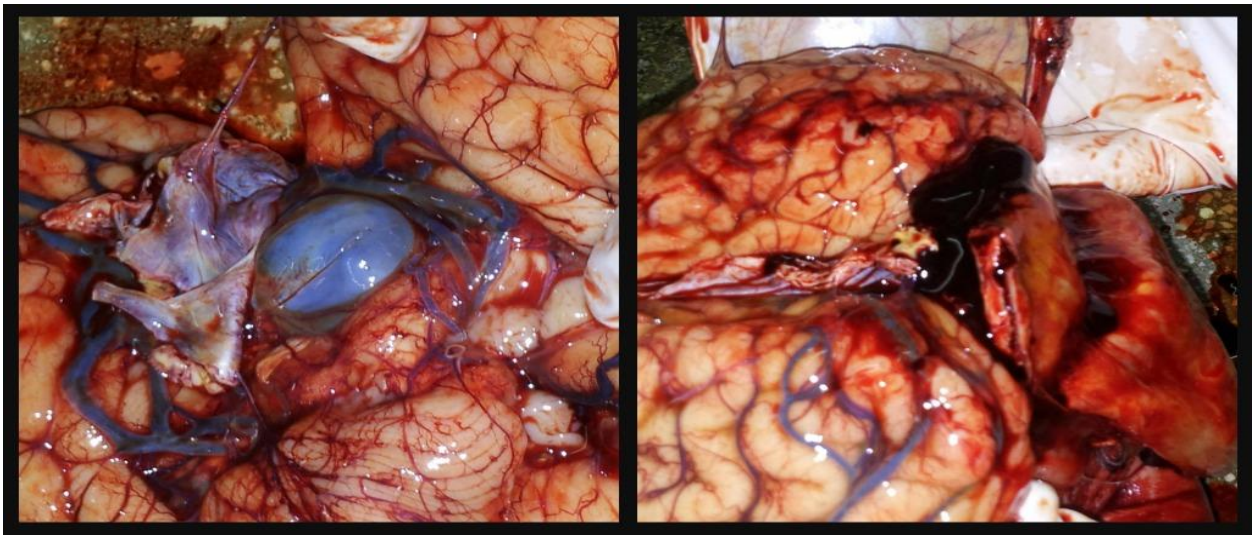

Figure 10. Macroscopy – Rupture of Galen vein aneurysm, hemorrhage.

Discussions

The aneurysm of Galen vein was first described in 1937 by Jager. Until 1984, less than 200 cases have been reported in the literature. Doppler ultrasound has allowed the first prenatal diagnosis. Galen vein aneurysm is a vascular malformation of choroid plexus. Due to the increased flow and turbulence, the vein wall is hypertrophied. Normally, Galen vein venous drainage is directed by sagittal sinus, but in some cases, thrombosis may be missing. The phenomenon of "stealing" is produced because the shunt, with the consequence of cerebral area hypoperfusion. (5,6). The placenta protects the fetus in the fight against the aneurysm, because it has a low resistance, so the amount of blood that reaches the aneurysm is also reduced and congestive heart failure is absent. But if the shunt is major, the placenta cannot compete with aneurysm, and cardiomegaly and fetal hydrops with brain damage may occur. Galen vein aneurysm prognosis depends on many factors, but the size of the aneurysm is not correlated with prognosis. The following factors: structural brain defects, dilated tract drainage, hydrops, dilated jugular vein, superior dilated vena cava, aortic retrograde flow, cardiomegaly, are correlated with a poor prognosis at birth. In utero, few cases are diagnosed Galen vein aneurysm. Forty percent are diagnosed in the neonatal period, the rest being diagnosed much later. (7,8). Antenatal diagnosis is performed after 30 weeks of gestation because malformations develops with increasing age of gestation and therefore pregnancy ultrasound in the third trimester is of utmost importance. In our case, all the ultrasounds examinations performed before 34 weeks of pregnancy couldn't detect the aneurysm. The differential diagnosis is performed with arachnoids cyst and porencephaly cyst. All these entities do not show color Doppler flow inside. Studies have shown that 77% of untreated cases evolve to death. But even if some cases benefit from surgical treatment, the mortality rate remains also high, around 39.4%. Treatment consists in blocking arterio-venous fistula flowing into the vein of Galen, thus reducing blood flow in the vein. (9,10). Open surgery has a high rate of morbidity and mortality, but recently, the endovascular embolisation is prefered.Unfortunately, in our center this technique is not available, and the case was quickly complicated by heart failure and cerebral hemorrhage and died before we managed to organize a transfer. (11,12).

Conclusions

The widespread use of routine prenatal ultrasound, allowed detection in the third trimester, of several cases of aneurysm of Galen vein. Useful in identifying the anomaly and its differential diagnosis from other lesions with space replacement, Doppler ultrasound is useful in fetal cardiovascular assessment, establishing the gravity of the case. (13).

Ultrasound diagnosis of these malformations facilitated postnatal therapy, greatly improving prognosis. In conclusion, Galen vein aneurysms and its possible complications can be detected by ultrasound and prognostic indices are useful in choosing the best therapeutic alternative.

Prenatal ultrasound identifies an anechogenic formation localized behind the third ventricle, but color Doppler examination is useful in differentiating aneurysm of Galen vein from other cystic median lesions. The same investigation can detect also the complications, such as congestive heart failure or those localized in the brain: cerebral hemorrhage, hydrocephaly.

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DIAGNOSIS MANAGEMENT STRATEGY OF DUCHENNE MUSCULAR DYSTROPHY

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Abstract

Duchenne Muscular Dystrophy (DMD) – an X-linked recessive inherited disease affecting around 1 in 3600 - 6000 male newborns – is considered the most severe human neuromuscular disease with no cure. It's determined by a mutation of the dystrophin gene DMD (Xp21), which codes for the dystrophin protein. The aim of gene therapy is to targeting the underlying genetic abnormalities, as the only chance for DMD patients to improve the quality of life and to increase the lifetime.

Generally, the diagnosis of DMD might be easily established on the basis of the family history, specific muscular symptomatology, elevated CK level, immunohistochemical examination and molecular testing. Though, lacking of family history, mild clinical features and laboratory technique limitations could delay the diagnosis of DMD.

A fast and definite diagnosis (molecular testing included) could offer the possibility to include the patients in international clinical trials focused on specific mutation, changing thus the evolutiv prognostic of disease.

The present work is trying to validate the minimum standards for a fast and complete diagnosis of Duchenne Muscle Dystrophy which would allow the same prognostic perspective for the Romanian patients.

The study was performed on 8 patients, using clinical evaluation, creatine phosphokinase dosing, immunohistochemical examination and molecular analysis.

The results of our study prove that some clinical features, such as phenotypic combination of Gower`s sign and calf hypertrophy might be high significant for DMD clinical diagnosis. Diagnostic certainty needs further explorations: the immunohistological examination (essential for the differential diagnosis), as well as the molecular analysis which confirms the diagnosis and allows, according to the mutation type, the inclusion in a targeted therapeutic study.

Key words: Duchenne Muscular Dystrophy, diagnosis management, therapy

Introduction

Duchenne Muscular Dystrophy (DMD), an X-linked disease that affect 1 in 3600-6000 live male newborns, is the most common muscular dystrophy present in early childhood, for which a curative treatment is not yet developed.(1).

Affected individuals present proximal muscle weakness and calf hypertrophy, usually manifested between 3 and 5 years of age. The disease is rapid progressive and most of the patients become wheelchair-bound by the age of 12. Respiratory, orthopedic and cardiac complications emerge and the boys die in their late teen to early twenties (2).

DMD occurs as a result of mutations in the dystrophin gene (DMD, locus Xp 21), which lead to an absence of dystrophin in the muscles. A milder form of DMD, Becker Muscular Dystrophy (BMD) is caused by allelic variants of DMD gene, which exhibit a less severe phenotype and evolution than DMD (BMD individuals can survive till their 7th decade (3).

A diagnosis of DMD can be made based on familial history, clinical symptomatology and creatine kinase level (4).

Males suspected to have a DMD based on these explorations need to be referred for molecular confirmation, which is achieved by demonstrating the presence of a pathogenic variant in the DMD gene. Sometimes, due to technical limitations, the mutation cannot be identified; in these cases, dystrophin analysis by immunohistochemistry from a muscle biopsy might be needed in order to establish a definite diagnosis (5).

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Material and methods

Our study shows the diagnosis pathway for 8 male patients between 4 months and 8 years of age, coming from Pediatrics and Neurology clinics and addressed to the Medical Genetics Department of University of Medicine and Pharmacy of Craiova for DMD suspicion. For all patients a thorough genetic examination was performed, consisting in achieving the family tree, detailed disease history, clinical and paraclinical examination.

Results

Of all 8 patients, only 2 have presented a family history for clinically and histopathologically confirmed muscular dystrophy highly suggestive for DMD.

Due to the way of suspecting the DMD diagnosis, the patients were divided in two groups:

- 2 patients with very elevated plasma levels of CK (20 – 100 times normal)
- 6 patients with clinical features characteristic for DMD. (Tab.1).

Apart the clinical features mentioned in Tab. 1, physical examination has revealed for all patients, except P1 – too young to offer a relevant clinical findings – a progression of the disease with a symmetric increase of muscle weakness and atrophy (more evident proximal than distal), lumbar hyperlordosis, waddling gait – Trendelenburg, Achilles contractures.

At that moment, no patient presents any sign of impairement of upper limb muscles, or cardiac and respiratory involvement. For 7 patients (P2 –P8) supportive investigation that molecular analysis of the dystrophin gene were performed; muscle biopsy with immunohistochemical study for dystrophin was performed in for P2 - P8 patients; patient P1 was already having this analysis at the time of presentation.

All patients (including P1) exhibited a negative immunohistochemistry stain for dystrophin (Dys -1, Dys – 2, Dys-3) (Tab. 1). The samples were analyzed for identifying the mutations for the dystrophine gene through various techniques, such as: multiplex PCR, MLPA analyse of genomic DNA by direct sequencing or by next generation sequencing. The results are shown in Table 2, allowing to classify all our patients from the study as DMD.

Disscutions

DMD clinical diagnosis should be easily made in the context of characteristic clinical presentation. The mean age of diagnosis of boys with DMD, without a family history of DMD, is around 5 years, but the diagnosis can be suspected earlier because of the delay in attainment of developmental milestones (delayed walking or language achievement).

Initial symptoms might include frequent falls, difficulty in running, jumping, standing up from standing on the floor (Gowers' sign – "climbing up their legs"), and climbing stairs. The atrophy of pelvic muscles leads to a development of a lumbar lordosis. Toe – walking is a common feature of the disease, as well as the hypertrophy of calf (1, 6, 7).

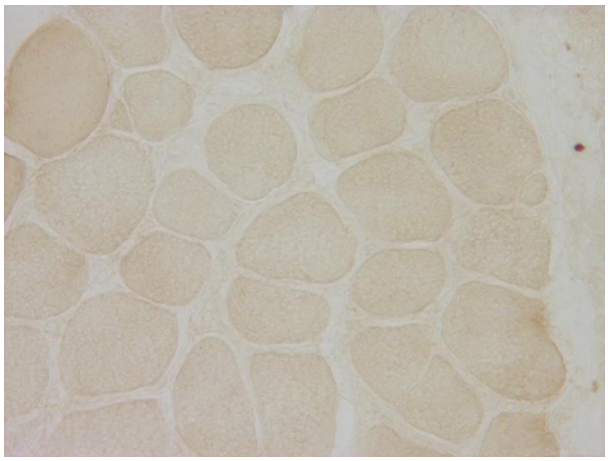

Fig. 1. Complete deficiency of dystrophin immunostaining on sarcolemm of the fibers from a patient of our study, x10.

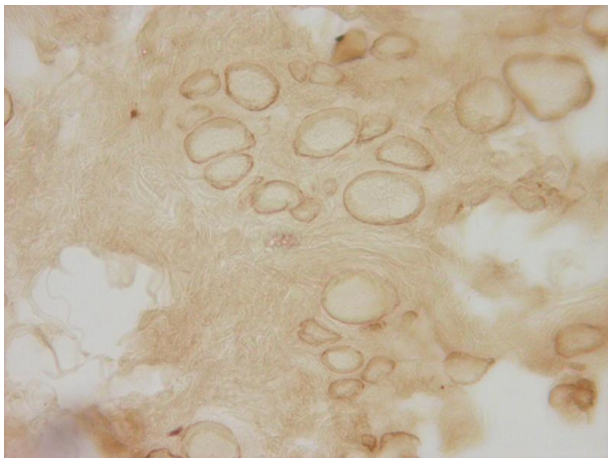

Fig. 2. Reduced dystrophin staining on sarcolem of the fibres from a control patient with BMD, x10.

The distinction between DMD and BMD is based on the symptomatology onset age (later-onset skeletal muscle weakness for BMD).

In keeping with its X-linked recessive pattern of inheritance, all the 8 patients of our study were males, and, except the P1, P2 and P8 cases, the age of initial presentation not different from those in other reports.

Table 1. Summary of clinical and paraclinical data for studied cases.

Patients	Family history	CK (U/l) serum level	First medical presentation age	First symptoms noticed	Age of first DMD diagnosis
P1	No	8500	4 months	- no clinical symptoms	4 months
P2	No	4320	2 years	- no muscular symptoms	2 years
P3	Brother	9300	3 years	- delayed walk - calf hypertrophy - difficulty to walk (slower than peers), to running, climbing stairs - frequent falls - Trendelenburg gait - hepatosplenomegaly	3 years
P4	Cousin of maternal grand mother	23451	4 years	- language delay, behaviour and cognitive problems - calf hypertrohy - difficulty to climbing stairs, to jump, and to run - muscular fatigability - Gower`s sign present	7 years
P5	No	6615	4 years	- delayed walk - calf hypertrophy - difficulty to climbing stairs, to jump, and to run - muscular fatigability	5 years
P6	Brother	7540	5 years	- delayed walk - calf hypertrophy -difficulty to walk (slower than peers), to running, climbing stairs - Gower`s sign present - Trendelenburg gait - hepatosplenomegaly	5 years
P7	No	18619	6 years	- delayed walk - calf hypertrophy - Gower`s sign present - Trendelenburg gait - toe walking	6 years
P8	Maternal oncle Maternal cousin	7385	6 years	- delayed walk - difficulty with climbing stairs, running - frequent falls - Gower`s sign present - calf hypertrophy - toe walking	8 years

CK – creatine kinase, DMD – Duchenne Muscular Dystrophy

Table 2. Results of IHC examination and genetics tests performed for including study patients.

Patients	Dystrophin evaluation by IHC	Molecular techniques used for DNA analysis	Mutations	Diagnosis
P1	Absent	Multiplex PCR	Del 45	DMD
P2	Absent	MLPA	Del 48-50	DMD
P3	Absent	Sequencing	ND	DMD
P4	Absent	Multiplex PCR	Del 46 – 47	DMD
P5	Absent	MLPA	Del 46 – 48	DMD
P6	Absent	Sequencing	ND	DMD
P7	Absent	MLPA	Del 51	DMD
P8	Absent	NGS	Nonsense mutation of exon 41	DMD

IHC – immunohistochemistry, PCR- polymerase chain reaction, MLPA – multiplex ligation-dependent probe amplification, ND – not detected, DMD – Duchenne Muscular Dystrophy

For 6 of the patients, symptomatology onset was between 3 and 6 years of age, with: difficulties to run or jump properly, frequent falls down, muscle fatigability, proximal muscle weakness (Gower`s manoeuvre present), calf hypertrophy. For all these patients we could notice a middle delay of walk (16 - 19 months old). They all had a normal neuropsychological and motor development in early childhood; the patient P1 had a normal evolution for his age (4 months) and the P4 patient had a language delay as well as behavior and cognitive problems. For 2 of the patients there was not an obvious clinical debut, the suspicion for a DMD diagnosis being based on random elevated levels of transaminases and further of the CK. Surprisingly, cases P4 and P8, with presumed DMD family history, are the latest patients evaluated in terms of age (seven and, respectively, eight years old), although both have presented specific clinical features and high levels of CK from early childhood. Thus, we can discuss about lacking of pathology approach in family, even without a diagnostic certainty in ancestry. For case P3, the diagnosis of his brother, case P6, was a trigger to early initiate the diagnosis protocol, part of exploration being assessed simultaneously for both, with a lower psychological impact on family.

Laboratory investigations were performed by several methods: biochemical analysis, DNA analysis, and histological examination.

Creatin kinase (CK) serum level

The characteristic finding in DMD is a noticeable increase of CK level. The normal serum level of CK varies with age, sex, and physical activity and may be elevated in several type of neuromuscular disorders (spinal muscular atrophy, myositis or other muscular dystrophies such Limb Girdle Muscular Dystrophies). In DMD occurs the most spectacular elevation of serum CK (50-100 times normal), even in newborns and prior to any symptoms (2, 6). Very elevated CK serum levels detected in our patients (4000 - 23000 UI/l) are at the highest point for literature existing serum levels and even if this is considered a non-specific DMD element, because of its association with other neuromuscular diseases, for two of our patients this was the first sign for a DMD diagnosis, due to their young age and lack of clinical features.

Genetic testing

Dystrophin gene is one of the biggest human genes (approximately 2.5 million base pairs, encoding 79 exons), so the molecular diagnosis for DMD can be complicated by the size of the gene and the multiple different mutation types (9). The majority of mutations in the DMD gene, accounting for 65% of cases of DMD and 85% of cases of BMD, is demonstrated to be deletions of one or more exons, especially in two "hot-spot" (mutation rich area) areas in the central genomic region (exons 2-20 and exons 45–53). The most frequent deletions, associated with DMD phenotype, in the literature, are those involving exons 45 (5, 3%), and 48-50 (5,1%) (10,11). Duplication of one or more exons accounts for 6-10% of cases of both DMD and BMD, and the remaining cases are due to point mutations, small insertions/ deletions or splice site changes. 2% of DMD cases occur by rearrangements and deep intronic changes.

The route to establish the molecular diagnosis depends on local availability of rapid and reliable testing and may include multiplex polymerase chain reaction (PCR), multiplex ligation-dependent probe amplification (MLPA), direct sequencing of all exons at the genomic level, or from cDNA of dystrophin gene. The two multiplex sets of Chamberlain et al. and Beggs et al. enable the detections of 98% of all DMD deletions. Even if the multiplex PCR is available, do not test all deletions, and do not characterize all deletion breakpoints (5, 10). The more recently developed MLPA technique is now the most widely used, since it will detect all whole exon deletions and duplications, and also characterize the end point of rearrangements at the exon level resolution (5). If MLPA does not reveal a deletion or duplication in DMD gene, the dystrophin gene sequencing should be done to search for point mutations or small deletions/insertions. Sequencing can be performed on either genomic DNA or on derived cDNA from muscle RNA. Complex rearrangements or deep intronic changes (approximately 2% of DMD mutations) will be not detecting using standards methods of genomic DNA analysis, and for these mutations the analysis of muscle RNA is required.

The next generation sequencing technique, recently developed, allows to sequence the whole gene, including introns, improved the probability of being able to detect the full spectrum of DMD mutations (5, 10). According to the lab possibilities were the tests were performed, 3 of the patients had the MLPA test, 2 of them had the multiplex PCR test, 2 patients benefited of sequencing analysis of DMD gene and 1 patient of next generation sequencing. In our study, two of patients had the most frequent deletions, associated with DMD phenotype (deletion of exon 45, and deletion 48-50), and the rest of them had deletions located in the two hot spot regions, of the dystrophin gene, described in the literature (Tab. 2). These findings are consistent with literature data, supporting the use of MLPA and multiplex PCR as first intention techniques for identifying dystrophin gene mutations. For P3 and P6 patients, even if the gene analysis was early carried, the mutation could not be identified, so additional RNA-based studies may be required in order to detect possible complex rearrangements, or variants located deep into the large introns of the gene. By chance, the only point mutation found in our cases was rapidly identified because the patient P8 was the only one who benefited by the NGS analysis as first approach.

Muscle biopsy

If a DNA mutation has been found, generally, a muscle biopsy is not needed any more for diagnosing DMD. But, when the genetic testing is not available in the centre where the patient is seen, if no mutation was identified, or if it is the case of a family history of DMD with unknown mutation, muscle biopsy can remain a routine investigation in DMD, and could be the only method able to establish a certain diagnosis (1, 2). Absent or markedly reduced dystrophin in muscles biopsies can be demonstrated by

immunostaining, using antibodies directed against different epitopes of dystrophin. As mentioned above, the immunohistochemistry continue to be the most specific method that can sustain a DMD diagnosis, and differentiate DMD from BMD (immunoreactivity is absent in DMD and significantly reduced in BMD) (2, 8, 12). For all our 8 patients immunostaing on muscle biopsy samples was performed. Sadly, since P1 and P2 patients had muscle biopsy previous to our study, we considered it as an impetuous act, due to their young age (4 months and 2 years, respectively). The others had immunohistochemistry for dystrophin on biopsy samples because of the impossibility of an initial genetic analysis or for exact setting of dystrophin deficit/absence, especially for the patients with a late presentation (6-8 years), for whom a differential diagnosis with BMD was to be considered. Dystrophin was entirely absent for all our studied patients. For 6 of them this was consistent with molecular analysis, while for P3 and P6 patients, with no identified mutation, this represented the main support for DMD diagnosis.

Even the size and distribution of expression of the dystrophin gene is challenging for the development of DMD therapies (10). Several experimental gene therapies are currently under investigation (8). Some of the most promising approaches to therapy for DMD, capable to convert DMD into a milder BMD phenotype: antisense oligonucleotide induced exon skipping, and non-sense mutation red-through, are targeted applied according to the mutation type (deletions, duplications, nonsens mutations (10). Because till now only corticosteroids offer a valid therapeutic benefit, we can say that no curative pharmacological treatment is available yet in DMD (6). Therefore, an earlier and complete diagnosis with genetic confirmation of the DMD mutation is crucial to identify patients eligible for experimental treatments (12).

Conclusions

A DMD diagnosis is one of the main diagnosis to be considered when we have a male patient with a delayed or abnormal global developmental (delayed walking and/or speech), early muscle impairment (calf hypertrophy, Gower`s sign, frequent falls), even doesn't exist a family history of DMD. A suggestive family history for DMD must be considered even in the absence of a certainty ascending diagnosis.

Significant family history for DMD should be considered, even without a diagnostic certainty in ancestry.

Finding an increase CK level (20 - 100 times normal), even if the patient is very young, represents a reason to immediately refer the patient to a specialist for confirmation of the diagnosis.

Actually, in the molecular diagnosis era, the muscle biopsy is no longer necessary, but it may be a very useful tool to establish the diagnosis in case when the genetic test could not identify any mutation. On the other hand, even if a molecular diagnosis is available, the immunohistochemical examination could differentiate DMD from BMD when the clinical phenotype is atypical.

If the experimental therapies in clinical trials based on targeted mutation proved their efficacy, it will be absolutely necessary to start this kind of treatments early, before significant muscle loss occurs, in order to obtain optimum benefits for the patients.

Thus, molecular diagnosis identification of the DMD responsible mutation is mandatory, impediments determined by technical or financial limitations must be overtopped by using a protocol for various genetic diagnosis techniques: (1) multiplex PCR for identification of deletions in deletional "hot-spots" of DMD gene, (2) MLPA, enable to detect all whole exon deletions and duplication, (3) sequencing of genomic DNA and cDNA or next generation sequencing for the other mutations (point mutations, small insertions/deletions, deep intronic changes, complex rearrangements)

An efficient testing strategy, whit a minimum rate of error, optimal for determining a quick and complete diagnosis could change the life prognosis for boys affected by DMD.

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THE SALT-WASTING TYPE OF 21-HYDROXYLASE DEFICIENCY: A CASE STUDY

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Abstract

The 21-hydroxylase deficiency is a monogenic disease, with a recessive autosomal transmission, which causes the disturbance of the synthesis of suprarenal corticoids.

We present the case of a newborn, aged 17 days, male, timely delivered, mother's fourth child, with a mixed feeding, who was admitted to 2nd Pediatric Clinic of the Emergency Hospital in Craiova with lack of weight gain progress and agitation. The baby presented, the following day after admission, severe dehydration syndrome with a hypovolemic shock, without any signs of fever, vomiting or diarrheic stools. We suspected the salt-wasting syndrome, which was later confirmed. Although the mother initially declared that her other three children were healthy, she later admitted that her first child, a girl, was diagnosed with 21-hydroxylase. Following an emergency treatment, of hydro-electrolytic balancing, and continued with a specific treatment, the evolution was favorable.

Key words: 21-hydroxylase deficiency, salt-wasting, newborn, male

Introduction

The 21-hydroxylase deficiency is a disease with recessive autosomal transmission, which causes the disturbance of the synthesis of corticosuprarenal steroids (1, 2). The dysfunction of the 21-hydroxylase enzyme causes an inefficient synthesis of cortisol and aldosterone and an androgenic overproduction (1, 2).

The disease presents three clinical types: two classic types (the salt-wasting and the simple virilizing ones) and a non-classic type with late onset (1). The two classic types are characterized by the virilization of the external genitalia, early, heterosexual pseudo-puberty and sterility in girls, and by isosexual, precocious pseudo-puberty in boys, together with a hypo-height tendency in boys and girls alike. To these changes which are present in the salt-wasting type, we can also add metabolic decompensations which present polyuria, hypotonic dehydration, hyperkalemia and metabolic acidosis, with an unfavorable evolution if no specific treatment (2).

Description of case

The newborn R.F., aged 17 days, was admitted to the 2nd Pediatric Clinic of the Emergency Hospital in Craiova (Medical History 44971/2011) accusing lack of weight gain progress, scleral-tegumentary jaundice and agitation.

Heredocolateral antecedents: young, healthy parents; three siblings: two brothers aged 10 respectively 8 years, and a sister aged 11 years and 6 months, who were healthy, without any chronic diseases within their family.

Personal physiologic antecedents: the fourth child, full-term delivery at the Emergency Hospital in Craiova, normal birth, head-down position, 3,500 g in weight, 52 cm in height, with no sufferance at delivery, Apgar score 9, presenting jaundice three days after birth; sent home when three days old, 3,200 g in weight, with a mixed feeding after two weeks of life (adapted milk powder formula); vaccinated in the hospital BCG and antihepatitis B; he received Vigantol Oil (2 drops per day), as a prophylactic measure.

Life conditions: a house in the urban area, adequate conditions, 7 rooms, 12 people.

Anamnesis. The mother notices her son's lack of weight gain progress after she leaves the hospital, the persistence of the tegumentary jaundice, agitation, and she decides to return to hospital.

At admission the newborn had no fever, with a fair general state, G=3,200 g, T=53 cm, SC=0.14 m^2, teguments and mucosae with intense jaundice, elements of folliculitis on an erythematous ground at the upper abdominal level, abdominal cutaneous creases with diminished elasticity, perioral cyanosis, nasal obstruction, the presence of bilateral vesicular murmur, feeble, slow heart beats, cold extremities, lingual mycotic deposits, normotensive anterior fontanelle 2.5/2 cm, the presence of the Munro reflex, a light, generalized hypotony, breastfed, without congenital malformations when objective exam.

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Investigations: Hemogram: Hb=18.9g%, T=398000/mm^3, L=15900/mm^3, NS=32%, Ly=61%, M=7%. Normal urine summary exam. Negative uroculture. Total bilirubin = 17.94 mg%, Direct bilirubin= 0.7 mg%, Indirect bilirubin= 17.24 mg%, proteinemia= 8 g%, urea= 30 mg%, creatinine= 0.74 mg%, glycemia= 49 mg%, GOT= 52UI/l, GPT= 17 UI/l. Chest ultrasound with no modifications. Cardiac ultrasound: patent foramen ovale. Normal abdominal ultrasound. ORL exam without modifications. Back part of the eye examination: normal aspect. Sucking test 70-80 ml of mother's milk per meal.

We proceeded to a treatment with phenobarbital p.o., oral bandage with glycerin and stamicin, oral treatment with baneocin for cutaneous lesions.

The next day after admission, the newborn showed stressed hypotony, sleepiness, abdominal cutaneous creases, cold extremities, slow heart rate, he refused to be breastfed; had no vomiting signs or diarrheic stool. We performed an urgent endovenous perfusion with normal saline solution, glucose and electrolytes, leading to an improvement of the general state. The dehydration syndrome with a hypovolemic shock was not caused by fever, vomiting or diarrheic stools; under these circumstances, the renal salt-wasting syndrome was taken into account. The serical ionogram which was performed when the acute dehydration syndrome appeared showed hyponatremia (Na=105 mEq/l), hypochloremia (Cl=83 mEq/l) and hyperpotassemia (K=5.9 mEq/l). When anamnesis, the mother said she had a niece with the diagnosis of 21-hydroxylase deficiency. The mother was once again asked if, within her family, there were relatives with 21-hydroxylase deficiency, and this time she admitted that her first child, a girl aged 11 years and 6 months, who was diagnosed with 21-hydroxylase deficiency, virilization type, was monitored by the Medical Genetics Department of the Emergency Hospital for Children in Cluj-Napoca.

We continued the investigations for the serum ionogram (table 1), the Astrup method and other specific tests in order to diagnose the 21-hydroxylase deficiency. Astrup parameters: pH= 7.39-7.26; pCO_2= 36.2-32.4 mmHg. 17-OH progesterone= 9.01 ng/ml (normal values= 0.8-5 ng/ml). Testosterone= 348 μg/dl (newborn normal values= 75-400 μg/dl). Aldosterone= 316 pg/ml (newborn normal values= 5-160 pg/ml). Cortisol= 2.09 ng/dl (newborn normal values = 3-20 ng/dl). Diuresis= 310-420 ml.

On the basis of the anamnestic data, (a sister diagnosed with 21-hydroxylase deficiency), the clinical picture (lack of weight gain progress and the onset of an acute dehydration syndrome, without vomiting and diarrheic stools), and the paraclinic data: ionogram with hyperpotassemia, hyponatremia, hypoglycemia, metabolic acidosis, combined with other specific data (highly increased 17-OH progesterone, low serum cortisone), we set the diagnosis of salt-wasting type of 21-hydroxylase deficiency to a male newborn (with no genitalia anomalies).

Table 1. Serum Ionogram.

Date	Na (mEq/l)	Cl (mEq/l)	K (mEq/l)
09.09.11	104	79	7
11.09.11	105	65	5.9
12.09.11	83	65	4.8
13.09.11	112	89	5.5
14.09.11	128	92.4	7.3
15.09.11	129	90	4.5

The treatment continued with an endovenous perfusion with glucose, NaCl 5.8%, calcium gluconate 10%, and hydrocortisone hemisuccinate i.v., then with Prednisone p.o and Astonin p.o., a treatment which was decided after the telephonic recommendations of Professor Dr. Paula Grigorescu Sido, from the Medical Genetics Department of the Emergency Hospital for Children in Cluj-Napoca.

Under treatment, the general state gradually improved, the newborn accepted to be fed, he gained 150 g in weight, good heart beat, AV=130/min, the tegumentary jaundice gave up (total bilirubin=1.92 mg%, direct bilirubin=0.34%, indirect bilirubin=1.58%). After 14 days of hospitalization, the patient transferred to the Emergency Hospital for Children in Cluj-Napoca, Medical Genetics Department, where the 21-hydroxylase deficiency diagnosis was confirmed. At present, he is under treatment with Hydrocortisone and Astonin p.o., with a favourable evolution.

Discussions

The classic type of disease appears in 1 out of 15,000-20,000 births for most of the populations; approximately 70% of the affected children present the salt-wasting type (3).

The gene which is responsible for the synthesis of 21-hydroxylase enzyme is located on the short arm of human chromosome 6, next to the genes of the major histocompatibility complex (1, 2).

The various mutations of the gene cyp-21 lead to faults of variable intensity at the level of the 21-hydroxylase enzyme, and consequently there are types of disease of different severity (3). In the severe, salt-wasting types, both aldosterone and cortisol are deficient because both hormones require 21-hydroxylase for their synthesis (3, 4). The alteration of the negative feed-back circuit of the corticosuprarenal leads to disturbance of the corticotropic hypophysis combined with the stimulation of cortisol

synthesis, proximal to the enzymatic block and with the deviation of the steroid synthesis through alternative pathways and androgenic overproduction, which is responsible for the feminine pseudohermaphroditism (4).

This disease frequently starts in the third week of life, as it happened with our case and, without a quick mineralocorticoid and glucocorticoid substitutive treatment, the evolution is fatal because of the hypovolemic shock or heart failure due to hyperkalemia.

The diagnosis is more difficult to establish in boys because they have their external genitalia clinically healthy; because the evolution of the disease is rapid, the boys who present genital anomalies are more likely to decease than the girls (5). That is why many countries decided to start the newborn screening, for this disease, from the 3rd-5th day of life, through doses of 17-OH progesterone in the capillary blood (6). Finding the heterozygotes is recommended in the families where there is one patient with 21-hydroxylase deficiency (2,6).

Paraclinic examinations

The hormonal examinations are necessary both for plasma (17-OH progesterone, ACTH, 21-deoxicortisol, testosterone, and 17-OHpregnenolon) and for urine (17 cetosteroids). The specific hormonal diagnosis criterion is represented by the increased concentration of 17-OH plasmatic progesterone (the metabolic substrate used by 21-hydroxylase) (6, 7).

Radiologic examinations: the fist x-ray to determine the child's bone age.

The ultrasound examination visualizes the corticosuprarenal glands, the girls' internal genitalia and the boys' testicle.

Genetic examinations: the Barr test and the karyogram which certify the genetic sex.

Genetic molecular examinations to determine the genetic mutation and its severity type (2, 3).

The prenatal diagnosis is possible in the first pregnancy trimester when using the analysis of the DNA which is obtained through the corial vilosities biopsy or in the second trimester through amniocentesis. It is recommended in the families where there is already an affected child and the prenatal treatment could be necessary (8).

Treatment

1. The chronic hormonal treatment aims at the substitution of glucocorticoids and mineralocorticoids (2, 4).

Glucocorticoids are used to compensate the cortisol deficit. The treatment also suppresses the excessive production of androgen hormones by the suprarenal cortex. We have used hydrocortisone 15-20 mg/m^2/24 hours, orally, in 3 shots; double or triple doses are recommended in infections and surgical interventions.

Mineralocorticoids: we used 9 α-Fluorocortisone (Astonin) 0.05-0.1 mg/24 hours, orally, in one single dose; they are recommended, first of all, in the salt-wasting form, but they are also used in the simple virilizing type.

2. The corrective surgical procedure of the external genitalia is required only in females, where pseudohermaphroditism may appear (8).

3. The psychological treatment addresses both the parents and the patients who must understand the nature of the disease and the role they have when aiming at a favorable evolution.

4. The prenatal treatment: besides the genetic counseling, the main objective of the early diagnosis is to facilitate an adequate, prenatal treatment to the affected women. Mothers with pregnancy at risk will receive dexamethasone, a steroid which crosses the placenta, 20 μg/Kg in 2-3 shots. Dexamethasone suppresses the steroid secretion by the fetal suprarenals, including the androgen secretion. If the treatment starts from the sixth week of pregnancy, the virilization of the external genitalia in the affected girls diminishes (9). The biopsy from the corial vilosities is performed to get the fetus genotype, the treatment being continued only if the affected fetus is a female (10). The DNA analysis of the fetal cells isolated from the maternal plasma in order to determine the sex and to analyze the gene cyp21 could allow the early identification of the affected female fetus (10).

An easier and earlier diagnosis would have been established for this case if the mother had declared, the moment she had been admitted, that she had one more child with a 21-hydroxylase deficiency. Although the mother was informed, when she had her first child with a 21-hydroxylase deficiency, that her future children were at risk, and that she could ask for a prenatal diagnosis of the disease, she disregarded these recommendations.

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SINONASAL MALIGNANT TRANSFORMATION OF SQUAMOUS METAPLASIA

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Abstract

Introduction. The aim of this study was to correlate the mother's biological status and related extrinsic factors during pregnancy and growth retardation and anemia in neonates. Material and method. We have done a prospective study on 75 mothers who delivered in 2013 in Obstetrics and Gynecology Clinics of Emergency County Hospital Timisoara and their newborns. Maternal extrinsec factors pre- or during pregnancy were related with the percentage distribution of neonates with IUGR and anemia. Results. Smoking habits (53%), lack of education (44%) and precarious socioeconomic conditions (42.7%) were the first three extrinsec factors well represented. The percentage distribution of newborns was 43% AG Sinonasal squamous cell carcinomas are relatively uncommon, representing only 3% of all head and neck malignancies. The treatment modality (surgery, radiotherapy, chemotherapy) poses several challenges. First of all, the patients are often diagnosed with advanced stage disease. Secondly, close proximity of critical structures and complex anatomy of the region, compromise surgical removal and radiation deliverance. Thirdly, important uncertainty issues surround fundamental aspects of treatment hence the optimal therapy protocol remains to be determined. We present an 18-year-old male patient with right sinonasal non-keratinizing squamous cell carcinoma and hard palate, middle infraorbital area, middle cranial fossa space involvement. Admission clinical signs and symptoms were: recurrent sinusitis, right sinonasal tumor and bilateral cervical lymph node involvement. A biopsy was performed and sent to the Pathology Service. The specimen was prepared with the routine histological technique. On hematoxylin eosin slides, the lesion was polypoid showing a connective tissue core with seromucous acini and moderate quantity of inflammatory cells (neutrophils, eosinophils, lymphocytes, histiocytes). The overlying epithelium was pseudostratified, being composed of ciliated columnar cells and presenting areas of squamous metaplasia. From these zones, originated a malignant tumor formed by epithelioid cells, with eosinophilic cytoplasm and vesicular nucleus containing prominent nucleolus. The cells were disposed in sheets, surrounded by fibrous connective stroma. Moreover, as precursor lesion, at transition site between normal epithelium and malignant tumor, was noted severe dysplasia. The histopathological aspects were consistent with a non-keratinizing squamous carcinoma arising in a fibro-glandular polyp with concomitant severe epithelial dysplasia, as a precursor lesion.

The patient underwent radiochemotherapy for primary tumor and cervical lymph nodes metastases; at 12 months after treatment no recurrence was noted.

Keywords: Sinonasal squamous cell carcinoma, cervical lymph nodes, malignant transformation, squamous metaplasia, severe epithelial dysplasia

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Introduction

Sinonasal squamous cell carcinomas are relatively uncommon, representing only 3% of all head and neck malignancies. Together with adenocarcinomas, squamous cell carcinomas are associated with a number of environmental factors such as smoking and alcohol use, exposure to heavy metals such as chromium and nickel and with workers in the leather, textile, furniture and wood industries (1, 2, 3, 4, 5)

The patient with sinonasal squamous cell carcinoma always describes a long standing disease with unspecific symptoms such as nasal obstruction, nasal discharge, minor epistaxis, headache and/or facial pain, other patients are asymptomatic. In more advanced stages patients may present facial swelling, vision changes or neurologic deficits (3, 4, 5)

Clinical investigation usually shows an exophytic tumor that tends to be friable, ulcerated and necrotic with increasing tumor size. On the other hand, sinus tumors are well-circumscribed, expansive and erosive to adjacent bony walls (1, 3, 4, 5)

Sinonasal squamous cell carcinomas can originate from epithelium of nasal cavity and paranasal sinuses. Early diagnosis is sometime difficult due to non-specific signs and symptoms and similar to those of allergic reaction, nasal polyposis and chronic sinusitis. In differential diagnosis, the most frequent suspicioned is a schneiderian papilloma and, at younger patients, angiofibroma (6)

Usually, the patients with sinonasal carcinoma present to the physicians earlier than those with maxillary sinus mucosa tumor.

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From histopathologic point of view sinonasal tumors are include squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, melanoma, and esthesioneuroblastoma. Some of these histopathological subtypes correlate with specific clinical aspects and aggressiveness as sinonasal undifferentiated carcinoma (7, 8)

Because of earlier presentation to the physician, the prognostic is better for sinonasal carcinoma than those from nasal sinuses.

The mainstay of the treatment remains surgery with excision of the tumor in free margins.

Case presentation

The male patient GV, 18-year-old, was admitted on October 2012 in ENT Department, "Victor Babes" University of Medicine and Pharmacy from Timisoara with the following diagnosis: right sinonasal tumor with bilateral cervical lymph node involvement.

The patient is a student; he was a heavy daily cigarette smoker for the last 2 years (16 per day). No other comorbidities were associated.

Hospital admission symptoms and signs consisted in: permanent right nasal obstruction, mucopurulent nasal discharge, cheek paraesthesia, cephalgia. Clinical examination revealed: obstruction of the right nasal fossa by a polypoid mass, right sinonasal tumor with hard palate involvement and bilateral cervical lymph node masses.

0^0 nasal and rhinopharynx endoscopic exam showed an exophytic tumor mass extending from the right middle meatus, to the hard palate, right maxillary sinus, nasal septum and left nasal fossa.

Cranial contrast enhanced CT scan highlighted a non-homogenous tumor mass in the right maxillary sinus and right nasal fossa (invading the medial, inferior and anterior maxillary sinus walls and extension into the left nasal fossa)(Figure 1). Fluid accumulation in the ethmoid, frontal and sphenoid sinuses were also visible. Bilateral cervical lymph node masses of approximately 20 mm were present.

Blood tests revealed: low white blood cell count (6200/mm3) with neutrophilia (78.4%), lymphopenia (17.2%) and monocytopenia (4.4%), high erythrocytes sedimentation rate (88 mm/h), low red blood cell count (3.62 million per mm3), and low hemoglobin (10.6 g/dl) and hematocrit (33.6%) levels.

Biopsy was performed for diagnosis. The tissue specimens were processed according with the routine histological technique. The specimens were fixed in 4% v/v buffered formalin and paraffin embedded. Three micrometers thick serial sections were stained with hematoxylin–eosin (HE). Histopathologic evaluation was performed with Leica DM750 microscope and images were acquired using Leica DMshare system.

On hematoxylin eosin slides, the lesion was polypoid showing a connective tissue core with seromucous acini and moderate quantity of inflammatory cells (neutrophils, eosinophils, lymphocytes, histiocytes). The overlying epithelium was pseudostratified, being composed of ciliated columnar cells and presenting areas of squamous metaplasia. At this point, the diagnosis on histological grounds was Schneiderian papilloma with area of squamous metaplasia. Serial sections revealed areas of malignant epithelioid cells, with eosinophilic cytoplasm and vesicular nucleus containing prominent nucleolus. The cells were disposed in sheets and originated from squamous metaplasia, being surrounded by fibrous connective stroma (Figures 2 and 3).

Moreover, as precursor lesion, at transition site between normal epithelium and malignant tumor, was noted severe dysplasia (Figure 4).

The final histopathological diagnosis was consistent with a non-keratinizing squamous sinonasal carcinoma arising in a Schneiderian polyp with fibro-glandular core and concomitant severe epithelial dysplasia, as a precursor lesion. The excisional edges were free of malignant invasion. The tumor was classified as a pT4 lesion**.**

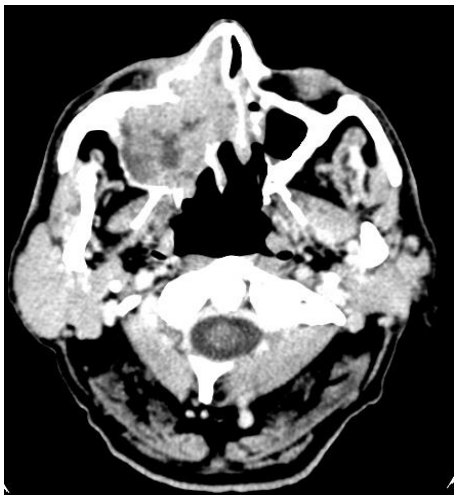

Fig. 1. A non-homogenous tumor mass in the right maxillary sinus and right nasal fossa, invading the medial, inferior and anterior maxillary sinus walls and extension into the left nasal fossa.

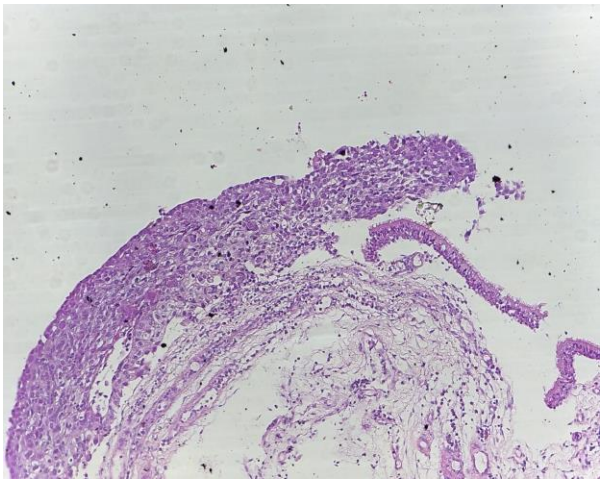

Fig. 2. Malignant cells originated from area of squamous metaplasia (left side), normal columnar ciliated pseudostratified epithelium of nasal cavity (right side), HE stain, ob. 4*

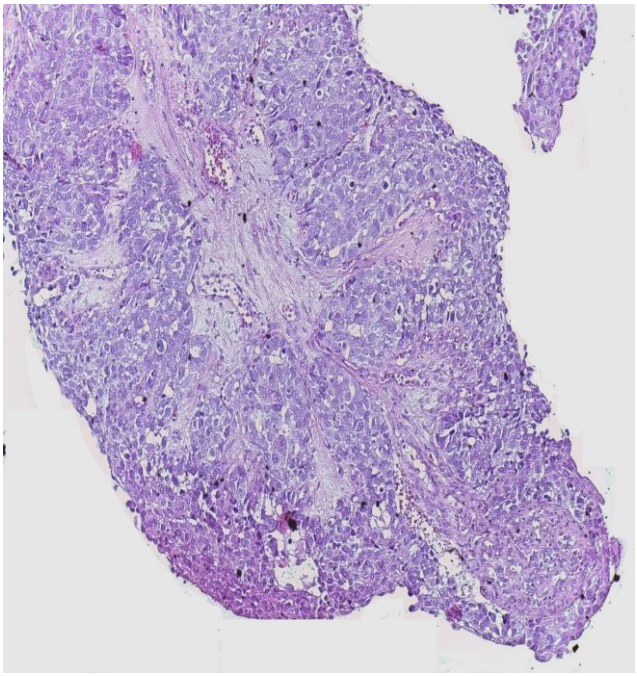

Fig. 3. Non-keratinizing squamous cell carcinoma of nasal cavity, HE stain, ob. 10*

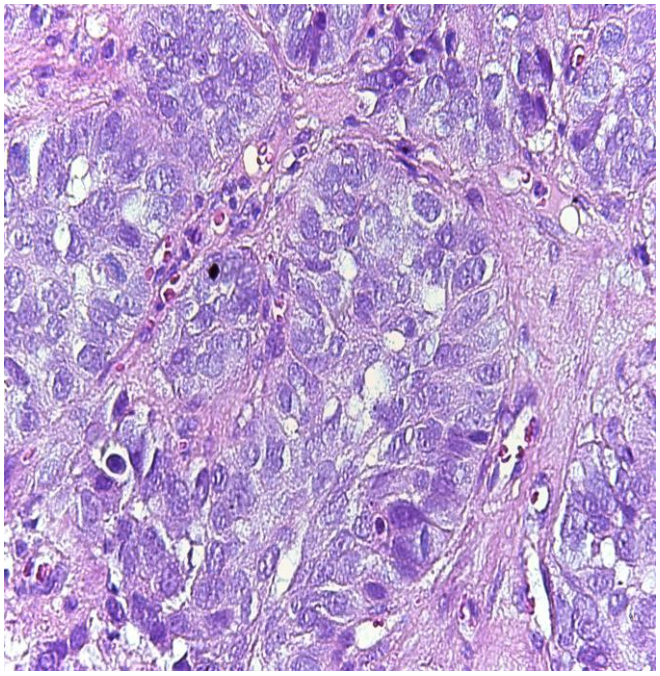

Fig. 4. Islands of malignant squamous cells with ample eosinophilic cytoplasm and vesicular nuclei, HE stain, ob. 40*

Discussions

The maxillary sinus (about 60%), the nasal cavity (about 22%), ethmoid sinus (about 15%) and frontal and sphenoid sinuses (<3%) are the most commonly sites affected by a sinonasal carcinoma. Unlike squamous cell carcinoma from other sites of head and neck region as nasopharynx, squamous cell carcinoma has a male predilection (2:1), with the highest incidence in the sixth – seventh decade of life (7)

Epistaxis is not uncommon and develops when the mucosa is ulcerated and the tumor extends to the medial sinus wall. Purulent and mucoid nasal discharge is also common due to secondary infection. Restriction of eye motility, diplopia or loss of vision and proptosis are present when the tumor affects the ethmoid, maxillary or frontal sinuses. Epiphora appears when the tumor affects the lacrimal sac or duct, cranial nerve involvement may also appear (1, 2, 3, 4, 5)

Late manifestations such as facial swelling and cheek paraesthesia, resulting from anterior maxillary extension into the soft tissue and infraorbital nerve involvement, are also common. Extension into the oral cavity forms a visible mass in the hard palate or alveolar ridge. Trismus can be caused by posterior extension, from the invasion of the pterygoid muscle. Auricular symptoms such as recurrent otitis media suggest possible involvement of the nasopharynx, eustachian tube and pterygoid plates. Extension into the skull base may lead to cranial nerve involvement, dura mater and intracranial invasion. It is rare to find cervical lymph node metastasis in early stages (1, 3, 4, 5)

The histopathological evaluation of excised specimen frequently reveals a squamous cell carcinoma either keratinizing or not. Other variants of squamous cell carcinoma as verrucous, papillary, basaloid cells, spindle cells, adenosquamous or acantholytic carcinomas are quite rare encountered in sinonasal region. The tumors are similar with their more frequent counterpart from the other sites of the body and can be well, moderately and poorly differentiated. The tumor cells are large, with eosinophilic cytoplasm and vesicular, nucleolated nuclei. Keratinization, were present, is observed at extracellular or intracellular level (dyskeratotic cells). The tumor cells are disposed in islands or small groups and, except for acantholytic subtype, are stabilized each to other with intercellular bridges. Frequently the tumor presents desmoplastic stroma. The tumor invades underlining tissues with cellular malignant strands (1)

As in our case, the tumor sometimes develops in a schneiderian papilloma or in area of squamous metaplasia, but precursor lesions for sinonasal carcinoma are by far less well defined as for oral or laryngeal counterpart. This feature is found in 10% of cases (1, 9)

Involvement of cervical lymph node appears in up to 20% of patients. Distant metastases are rare (1, 5).

If the sinonasal carcinoma is localized in the nasal cavity, the 5- and 10 year survival rates are as high as 80%, but extension to the paranasal sinus significantly lowers the survival rates (1, 3, 4, 10) Moreover, factors that predict a worse prognosis are advanced local disease and keratinizing histological subtype.

Treatment options include combination modalities of surgery, radiotherapy, and chemotherapy. Due to the low incidence and diverse histopathologic types it is difficult for a department to gain enough experience in the sinonasal tumors treatment (15).

Treatment failures mainly are related either to an advanced disease (T3 and T4) or to a tumor recurrence in areas difficult to access (skull base, dura and brain) (1).

M. H. Jakobsen et al. (11) do not support the advantages of combined treatment modality over a single treatment modality of RT or S.

Cervical lymph node metastases are generally associated with poor survival and high recurrence rate (12, 13, 14, 15, 16), being considered to be the most important survival prognostic parameter in squamous cell carcinoma group (11) and anemia in neonates (1). Improving educational opportunities, health-related behavior and access to health care (13) could reduce the risks and not ultimately different inequalities in health in the EU countries for instance (13).

Conclusions

The patient underwent radiotherapy for both sinonasal tumor area and bilateral cervical area, followed by chemotherapy. At 12 months after treatment there were no recurrence noted.

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A MODEL COMBINING PROCALCITONIN, C-REACTIVE PROTEIN AND URINALYSIS IS SUPERIOR TO INDEPENDENT VARIABLES FOR PREDICTING SERIOUS BACTERIAL INFECTIONS IN FEBRILE CHILDREN

Diana A. Moldovan[1,2], Maria D. Baghiu[1,3], Cristian Boeriu

Abstract

Introduction and aim. Fever is a common complaint for children addressing the emergency departments (ED). Distinguishing between febrile children with self limited viral infection and those with serious bacterial infection (SBI) may be challenging for practitioners, especially in younger population. Recently, a laboratory score, named the Lab-score, combining Procalcitonin, C-reactive protein and urine dipstick was developed for predicting SBI in febrile children. The Lab-score was further assessed and validated in several studies. We aimed to search current literature and evaluate its value per se and by comparison with independent variables. ***Method.*** We search electronically the literature, in Medline, Embase and Google Scholar and identified the articles directly related to the Lab-score. We analysed the results of each study selected and corroborated the data. ***Results.*** The search returned 773 articles, six of them being relevant for the study. The highest sensitivity for the Lab-score for predicting SBI was 94% (95%CI: 82-99) and the highest specificity was 95% (95%CI: 93-96). The highest performance found for the Lab-score was reflected by an AUC of 0.91 (95%CI: 0.87-0.93) and the lowest by an AUC of 0.73 (95%CI: 0.69-0.77). We found that in four studies the Lab-score performed significantly better than independent predictors associated with SBI. Two studies found similar prediction power comparing the Lab-score with independent variables, one assessing a small group of infants and one assessing a much broader age group than all other studies. ***Conclusions.*** The Lab-score is a valuable tool for predicting SBI in febrile children addressing to ED and superior to independent variables, particularly in younger groups. Further validations are required for stronger conclusions.

Key words: fever, children, C-reactive protein, Procalcitonin, Lab-score

Introduction

Fever, one of the main reasons children are brought in emergency settings1,2, has always been a concern for practitioners, especially when related to serious bacterial infections (SBI) such as urinary tract infection (UTI), pneumonia, bacteraemia, meningitis, sepsis. Particularly in young children, who often have fever without an apparent focus3, distinguishing between a self limited viral infection and an SBI may be challenging.

Diagnosis of SBI in febrile children, which was reported to be around 20%4, has been researched during the past years in relation with new biomarkers. Among many proposed, C-reactive protein and Procalcitonin proved strong prediction value in detecting SBI5-14. Recently, a laboratory index score, named the "Lab-score", combining PCT, CRP and urinalysis showed promising results for identifying SBI in children younger than 36 months with fever without source15. The Lab-score has already been assessed and validated in several studies16-20.

We aimed to assess the value of the Lab-score in identifying SBI in febrile children and whether the Lab-score performs better than independent biomarkers, namely PCT and CRP, by reviewing the existing literature on the subject.

Methods

The Lab-score was developed in 2008 by Galetto-Lacour et al15, and combines PCT, CRP and urine dipstick which were the only independent predictors contributing to a stepwise multiple logistic regression model predicting SBI in febrile children. According to the Lab-score, 0 points are attributed for PCT<0.5ng/ml, 2 points for PCT ≥0,05ng/ml and 4 points for PCT ≥2ng/ml; also 0 points are attributed if CRP is <40mg/l, 2 points if CRP value ranges between 40mg/l and 99mg/l and 4 points for CRP ≥100mg/l. 1 point is attributed for positive urine dipstick, that is if positive leukocyte esterase and/or nitrates. The Lab-score values range from 0 to 9, and the cut-off of ≥3 points was proposed as optimal for SBI prediction.

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Table 1. General characteristics of analysed studies

Study	Design	Number of participants	SBI (%)	Age range	Inclusion criteria	Outcome diagnosis
Galetto-Lacour, 2008[15]	Prospective, observational	202	27	7days-36months	Temperature (rectal) >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis
Galetto-Lacour, 2010[16]	Prospective, observational	406	22,7	7days-36months	Temperature (rectal) >38.0°C (7days-3months) and without localising signs of infection in history or at physical examination and temperature (rectal) >39,5^{0}C (3-36months) or toxic appearing	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, sepsis
Bressan, 2012[17]*	Retrospective	1012	28,3	less than 3 months	Fever (axillary or rectal) without localizing signs of infection	UTI, bacterial gastroenteritis
		1098	2,1	less than 3 months	Fever without localizing signs of infection	UTI and bacteraemia, occult bacteraemia, meningitis
Nijman, 2014[18]	Prospective, observational	1084	16	1month-16years	Temperature (rectal)>38,5^{0}C	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, osteomyelitis, cellullitis orbitae, erysipelas, bacterial gastroenteritis
Lacroix, 2014[19]	Randomized controlled trial	271	24,7	7days-36months	Temperature >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, osteoarthritis, bacterial gastroenteritis
Moldovan, 2015[20]	Prospective, observational	90	21,1	7days-12months	Temperature >38.0°C and without localising signs of infection in history or at physical examination	Bacteraemia, UTI, lobar pneumonia, meningitis, bacterial gastroenteritis, sepsis

SBI: serious bacterial infection

*Bressan et al[17] dichotomized sever infections in SBI and IBI (invasive bacterial infections). The authors included 1012 infants for SBI analysis and 1084 infants for IBI analysis. UTI and bacterial gastroenteritis were defined as SBI and occult bacteraemia, UTI and bacteraemia and meningitis were defined as IBI.

Table 2. Diagnostic value of CRP, PCT and the Lab-score for SBI

Parameter	Cut-off value	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR -(95%CI)
CRP					
Galetto-Lacour, 2008[15]	40	**81 (65-90)**	76 (67-83)	n.a.	n.a.
Galetto-Lacour, 2010[16]	40	73 (63-81)	81 (77-85)	3.8 (3.0-5.0)	**0.34 (0.24-0.47)**
Bressan, 2012[17]	n.a.	n.a.	n.a.	n.a.	n.a.
Nijman, 2014[18]	40	58 (50-65)	81 (78-83)	2.98 (2.47-3.58)	0.53 (0.44-0.63)
Lacroix, 2014[19]	n.a.	n.a.	n.a.	n.a	n.a.
Moldovan, 2015[20]	40	57 (33-79)	**94 (86-98)**	**10.27 (3.68-29)**	0.45 (0.26-0.76)
PCT					
Galetto-Lacour, 2008[15]	0,5	**94 (82-99)**	68 (58-76)	n.a.	n.a.
Galetto-Lacour, 2010[16]	0,5	75 (65-83)	76 (71-81)	3.1 (2.5-4.0)	0.33 (0.23-0.47)
Bressan, 2012[17]	n.a.	n.a.	n.a.	n.a.	n.a.
Nijman, 2014[18]	0,5	60 (52-67)	78 (75-81)	2.73 (2.29-3.24)	0.51 (0.43-0.62)
Lacroix, 2014[19]	n.a.	n.a.	n.a.	n.a.	n.a.
Moldovan, 2015[20]	0,5	78 (54-93)	**88 (78-95)**	**7.01 (3.50-14)**	**0.24 (0.10-0.57)**
Lab-score					
Galetto-Lacour, 2008[15]	3	**94 (82-99)**	81 (72-88)	4.92 (3.26-7.43)	**0.07 (0.02-0.27)**
Galetto-Lacour, 2010[16]	3	86 (77-92)	83 (79-87)	5.1 (3.9-5.5)	0.17 (0.1-0.28)
Bressan, 2012[17]	3	52 (46-58)	**95 (93-96)**	**10.2 (9.5-10.9)**	0.5 (0.5-0.5)
Nijman, 2014[18]	3	60 (52-67)	86 (84-88)	4.32 (3.53-5.29)	0.46 (0.39-0.56)
Lacroix, 2014[19]	3	85 (76-93)	87 (82-91)	6.68 (n.a.)	0.17 (n.a.)
Moldovan, 2015[20]	3	73 (48-90)	92 (84-97)	**10.43 (4.39-25)**	0.28 (0.13-0.6)

CRP: C-reactive protein, PCT: procalcitonin,; LR: likelihood ratio; n.a.: not available

Table 3. Area under the receiver operating characteristic curves for CRP, PCT and the Lab-score for SBI prediction reported in the analysed studies

Parameter	AUC (95%CI)
CRP	
Galetto-Lacour, 2010[16]	**0.86 (0.82-0.89)**
Bressan, 2012[17]	0.77 (0.73-0.80)
Nijman, 2014[18]	0.77 (0.69-0.85)
Lacroix, 2014[19]	0.83 (0.77-0.89)
PCT	
Galetto-Lacour, 2010[16]	**0.84 (0.80-0.87)**
Bressan, 2012[17]	0.73 (0.69-0.77)
Nijman, 2014[18]	0.75 (0.67-0.83)
Lacroix, 2014[19]	0.81 (0.75-0.87)
Lab-score	
Galetto-Lacour, 2010[16]	**0.91 (0.87-0.93)**
Bressan, 2012[17]	0.83 (0.80-0.86)
Nijman, 2014[18]	0.79 (0.72-0.87)
Lacroix, 2014[19]	**0.91 (0.87-0.95)**

CRP: C-reactive protein, PCT: procalcitonin,;
AUC: area under the receiver operating characteristic curve

We searched the literature electronically, in Medline, Embase and Google Scholar, using the key words associated with serious infections, fever, children, laboratory scores, emergency department. Studies were selected if they assessed the Lab-score value in predicting SBI in children, aged less than 16 years, with fever with or without a source. SBI were defined as UTI, pneumonia, bacteraemia, sepsis, meningitis, bacterial gastroenteritis, cellulitis, septic arthritis and osteomyelitis.

Results

The electronic search in Medline, Embase and Google Scholar, using the key words mentioned above in the Method paragraph, returned nearly 773 results, although, refining the search, we found only six articles directly relevant for our study. Besides the study which proposed the Lab-score, we found two studies which validated the original score, two studies which assessed the new method and one clinical trial which assessed the impact of the Lab-score on antibiotic prescription rate. The final number of studies analysed was six, comprising 3151 patients. The general characteristics of included studied are reported in Table 1.

All studies were carried in the emergency department. Except for one study17 which was retrospective, all studies enrolled patients prospectively. Presence of fever was an inclusion criterion for all studies. Five studies included children with fever without localizing signs of infection. One single study included children with fever with or without signs of infection, although excluded those patients with fever and a clear focus of an upper airway infection, considering them as having a very low risk of SBI.18 Three studies included children between 7 days and 36 months of age,15,16,19 one study infants less than 3 months17, one study infants less than 12 months20 and one study children between 1 month and 16 years.18 The outcome diagnosis of SBI included bacteraemia, UTI, pneumonia, meningitis (six studies), osteoarthritis (four studies), sepsis (two studies), osteomyelitis, cellullitis orbitae, erysipelas (one study). For the six studies analysed the prevalence of SBI ranged between 16% and 28,3%.

All studies included for analysis had CRP, PCT and urinalysis taken from all patients and the Lab-score calculated. In Table2 are reported the sensitivities, specificities and positive and negative likelihood ratio for the CRP, PCT and the Lab-score as found in the studies included in the analysis. The best sensitivity obtained for the Lab-score was 94% (95%CI: 82-99)15 and the best specificity was 95% (95%CI: 93-93)17.

Analysing the area under the receiver operating characteristic curve (AUC) we found better performance for the Lab-score in comparison with CRP and PCT in the analysed studies, where it was available (Table3).

Discussion

Structured approach and step wise decision making are of paramount importance for identification of children having serious conditions, as well as for safe discharge of those with minor illnesses, in EDs with increasing overcrowding. Recently, practitioners have taken the challenge to develop tools for identifying SBI in febrile children presenting in EDs by using the new surrogate biomarkers, especially CRP and PCT.15,21

The Lab-score, proposed by Galetto-Lacour et al15 in 2008, showed promising results and was already assessed and validated in several studies. The original study included two cohorts of children with fever without a source (FWS) prospectively enrolled from the same hospital, in Geneva, Switzerland. 202 children, age 7 days to 36 month, were analysed. The derivation population comprised 135 children and the validation population 67 children. 54 children (27%) from 202, had SBI. The performance of the Lab score was robust and similar in both populations with sensitivities of 94% (derivation set) and 94% (validation set) and specificities of 81% (derivation set) and 78% (validation set) at a cut-off value of $\geq$3.15 A systematic review published by Van den Bruel et al4 argued that from 14 studies assessing the value of laboratory tests for identifying SBI in febrile children, the Lab-score offered the best prediction rule for the purpose.

In 2010 the Lab score was externally validated on a cohort of 406 children with FWS age 7 days to 36 months from Padua, Italy.16 The performance of the Lab-score was similar (86% sensitivity and 83% specificity) and also better than for independent variables associated with SBI. The study supports the use of the Lab-score in clinical practice for identifying febrile children at risk for SBI, instead of the old models which included white blood cell count (WBC) which proved poor prediction for SBI. Nevertheless, recent data suggest that WBC should not be used currently as triage tool for febrile children for distinguishing between viral and bacterial disease.22

Bressan et al17 assessed the method on a retrospective study including 1098 infants less than 3 months, with FWS, from five Spanish and two Italian pediatric EDs. The population was analysed for SBI and IBI. A lower sensitivity for the Lab-score for SBI prediction was obtained by comparison with the original study. However, the authors proposed, in order to increase the sensitivity, lower CRP cut-off values and higher scores for PCT values between 0.5 and 2ng/ml. Fever duration was also proposed to be taken into consideration. However, the Lab-score proved significantly superior to independent variables for SBI prediction.

Nonetheless, Nijman et al21 , proposing a clinical prediction model which included the added value of CRP, as well as fever duration, offered a promising alternative for identification of SBI in febrile children. The model offered risk thresholds rather than a single cut-off level. In another study, Nijman et al18 also validated externally the Lab-score and proposed an updated model. The population included, comprising 1084 febrile children age 1 month to 16 years, was recruited from a university hospital's ED, from Rotterdam, The Netherlands. However, the results were intriguing, CRP and the Lab-score having a similar performance in predicting SBI, and both slightly higher than PCT. Nevertheless, as the authors argued, the population differed in age limits and this could interfere the results. The

updated model only modestly outperformed the original Lab-score. In addition, the same authors suggested a step-wise approach of febrile children, an idea also argued by Mintegi et al23 in a study on febrile young infants (less than 3 months).

We also performed a study in Tirgu Mures, Romania, in a university hospital's ED, assessing infants (less than 12 months) with FWS for SBI.20 We found robust performance for the Lab-score, but only slightly superior to CRP. However, the group study was rather small to make a definitive conclusion.

A randomized clinical trial, performed in the same center where the Lab-score was developed, assessed the impact of the Lab-score on the antibiotic prescription rate in children with FWS, age 7 days to 36 months.19 Testing the Lab-score prospectively was the second objective of the study. The Lab-score performed better than any other independent biomarker for SBI detection. The investigators argued that if the Lab-score would have been strictly used, a significant 26.5% reduction of antibiotic prescription rate would have been encountered.

From the six studies analysed there is evidence that the Lab-score is a valuable tool for identifying SBI in febrile children and superior to independent variables associated with SBI. It might be wiser though, to limit its use particularly in infants and young children with FWS, for whom the Lab-score was designed and who are more prone for SBI. The strength of the method is given by its easy-to-use pattern, while the cost of two biomarkers, PCT being more expensive, makes it less affordable for poor resource settings.

The main limitation of our study consists in the rather small number of studies included for analysis. Further external validations are required to draw more robust conclusions.

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INCIDENCE AND RISK FACTORS IN CAUSING RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS WHOSE MOTHERS RECEIVED PROPHYLACTIC CORTICOSTEROIDS

Andreea Fraţilă-Băbeanu[1*], Daniela Iacob[1]

Abstract

Respiratory distress syndrome is one of the most common respiratory diseases in newborns, especially premature infants.

The administration of antenatal steroids in women at risk of preterm birth is the most effective medication treatment. The goal of this therapy is to prevent respiratory distress syndrome and to reduce neonatal morbidity and mortality. Glucocorticoid therapy help accelerate fetal lung maturation by increasing production and elimination of surfactant.

A retrospective study was performed between January 1, 2011 and December 31, 2013 conducted in 197 premature infants whose mothers received antenatal corticosteroids.

Prevention of neonatal respiratory distress syndrome decreased the incidence of the disease or a milder appearance. Risk factors involved in worsening respiratory distress syndrome are low gestational age, low Apgar score, infections, caesarean section, male gender, etc.

Key words: neonatal respiratory distress syndrome, prematurity, prenatal corticosteroids, surfactant

Introduction

Neonatal respiratory distress syndrome is the most common cause of death among premature infants, due to lung immaturity more exactly surfactant deficit. The natural process of alveolar surfactant production begins early in fetal life and is mature after 34 weeks gestational age.

The incidence and severity of neonatal respiratory distress syndrome are inversely proportional to gestational age. The administration of corticosteroids to mothers predisposed of preterm birth, accelerate fetal lung maturation. This process is achieved by accelerating the production and release of surfactant in the lung alveoli.

Corticosteroid therapy is recommended for all pregnancy at risk of preterm birth less than 34 weeks gestation. Administration of corticosteroids may be indicated also after 34 weeks gestation, when there is evidence of pulmonary immaturity.

All women at risk of preterm birth should start treatment with antenatal corticosteroids, except for the case that birth is imminent (less than one hour). Glucocorticoids used are dexamethasone 6 mg, 4 doses every 12 hours or betamethasone 12 mg, 2 doses at 12 hours.

Objectives

This paper aims to highlight the incidence and severity of appearance respiratory distress syndrome, and factors that worsen in a group of premature infants whose mothers received prophylactic corticosteroids.

Material and Methods

The study was conducted at the Clinic of Neonatology "Bega" Timisoara for a period of 3 years, between 2011-2013.

From the total of 565 preterm infants with gestational age below 37 weeks, born during this period, have been introduced in study 197 premature infants whose mothers received prophylactic corticosteroids. Dexamethasone was administered 4 doses every 12 hours.

The work method was represented by retrospective analysis of patients observations papers. The study included infants whose mothers received prophylactic antenatal corticosteroids. They gathered data from each patient ,like: gestational age, sex, birth weight, Apgar score, birth mode, the severity of respiratory distress, need for ventilatory support, administration of surfactant associated infections, and patient evolution.

Results and discussion

Between 1 January 2011 and 31 December 2013, the Department of Neonatology "Bega" Timisoara, were born a total of 565 preterm, of which only 197 premature infants with gestational age below 37 weeks received antenatal corticosteroids.

The distribution of the premature baby per year was 2011-73 cases, 2012-34 cases, 2013-90 cases. We see an increase in performing prophylaxis of neonatal respiratory distress syndrome in 2013.

The distribution by gender was: 46% females versus 54% males. Premature coming by Caesarean section have a higher prevalence, 74% compared to those coming through natural birth.

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Another criterion was gestational age. Most cases were between 31-33 weeks - 39%, between 28 to 30 weeks - 26%, between 34-36 weeks - 24% and 25-27 weeks - 11%. (Fig. 1)

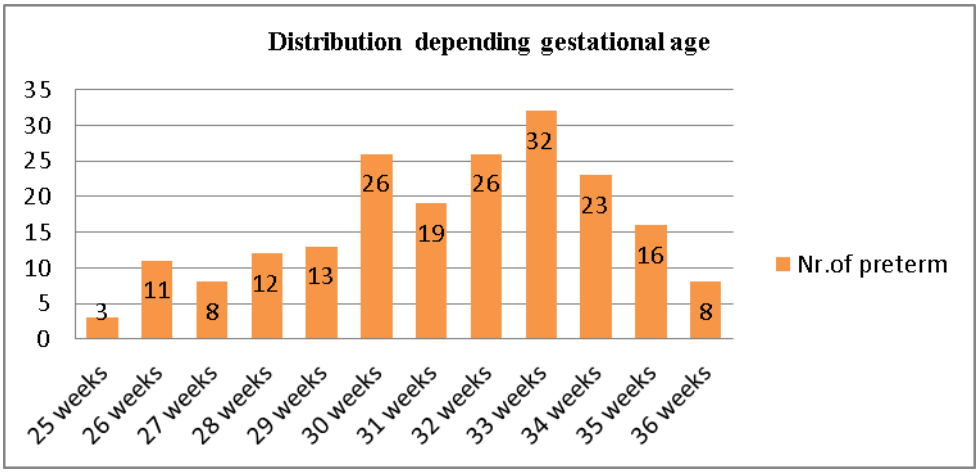

Fig. 1. Distribution of cases depending gestational age.

Distribution by birth weight. Under 1000g - 10%, between 1000g -1499g - 24%, 1500g, 1999g between - 37%, 2000g -2499 to 24% and over 2500g - 5%. It shows a higher prevalence between 1500 g- 1999 g.

The Apgar score is a very important criterion. In the studied group, preterm had at birth Apgar score between 1-3 17%, 4-6 - 33% and between 7-9 - 50%. Can be noticed that Apgar score between 7-9 has a higher prevalence.

Premature infants whose mothers received antenatal corticosteroids developed RDS severe form in 28% of cases the average form in 16% of cases, mild 16% of cases and 40% of them had no RDS.

In the cases that appeared respiratory distress syndrome, 59 premature required mechanical ventilation, 46 cases required nasal CPAP and 46 premature received surfactant.

Infections in preterm are diverse, they aggravate their evolution. Pathogens present in the highest proportion in the study group were: Candida albicans - 12 cases and 13 cases Staphylococcus coagulase- negative. (Fig. 2)

The presence of the infections increase the risk of respiratory distress syndrome and its gravity.

The evolution of premature is based on several issues. In our study group, the evolution has been favorable in 86% of cases and bad in 14% of cases.

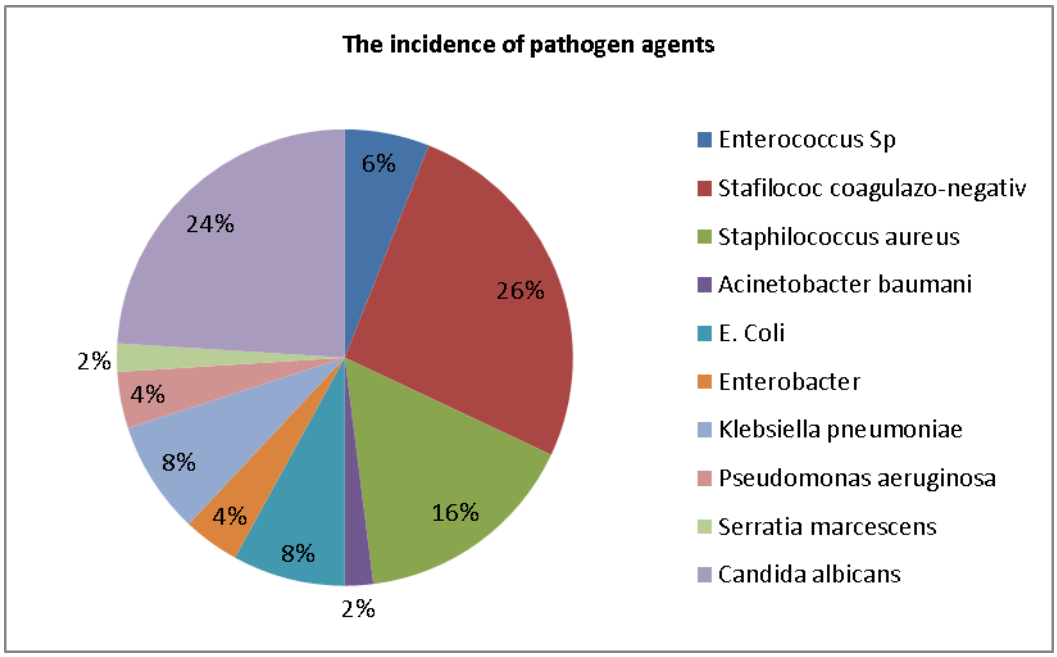

Fig. 2. The incidence of pathogen agents.

Conclusions

1. The administration of corticosteroids to pregnant women at risk of preterm birth lowers risk of respiratory distress syndrome.

2. The combination of risk factors: low gestational age, low birth weight, low birth Apgar score, presence of infections, caesarean section, increase the risk of RDS.

3. Most cases who received prophylactic dexamethasone were between 31-33 weeks.

4. The pathogens most commonly implicated in infections in preterm were Candida albicans and coagulase-negative Staphylococcus.

5. Pregnancy risk of preterm birth requires a rigorous monitoring so that they can make timely administration of corticosteroids.

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NECROTISING ENTEROCOLITIS – ETIOPATOGENIC FACTORS IN PREMATURE VERSUS TERM NEONATES

Elena Hanganu[1], S.G. Aprodu[1], Simona Gavrilescu[1], Andreea Avasiloaiei[2], Mihaela Moscalu[3], Maria Stamatin[2]

Abstract

Objectives. The aim of this paper is to analyze the elements that define the etipathogenical profile of NEC cases diagnosed in term and preterm neonates admitted in the Regional Center of Neonatal Intensive Care Unit "Cuza Voda" and "Sf. Maria" Emergency Children Hospital Iasi.

Matherial and methods. An analytic retrospective study was performed and all cases of necrotizing enterocolitis diagnosed in the Regional Center of Neonatal Intensive Care Unit "Cuza Voda" and "Sf. Maria" Emergency Children Hospital Iasi were included. A datasheet was developed for study group (premature) and control (term neonates) group and the statistical analysis of the 205 cases was performed in correlation with the following variables: gender, gestational age (GA), birth weight (BW), APGAR score, maternal and neonatal risk factors, the presence of associated anomalies, type of feeding, age, symptoms at onset and stage at diagnosis according to Bell criteria. The statistical analysis of all data was performed in SPSS Statistics 20 program.

Results. The incidence of NEC was 3.32%, with a total number of 205 cases identified: 155 cases in premature group and 50 cases in control group. In study group 65.81% were born naturally versus 46% in control group respectively 34.19% were born trough cesarean section versus 54% in control group. Birth weight was < 1000g in 12.9% of cases and < 1500g in 43.9% in the study group with only 14% below 2500g in control group. 98 cases were diagnosed in stage I Bell (63.23%), 46 cases in stage II (29.68%) and only 11 cases were diagnosed in stage III (7.1%). In study group 21.9% presented persistence of ductus arteriosus (PDA) whereas in the control group PDA was identified in 12%. Perinatal asphyxia was present in 17.42% of cases in the study group, mild respiratory distress in 32.9%, moderate distress in 27.1% and severe respiratory distress in 40%. Bacterial colonization was identified with a frequency of 45.2% whereas in the control group frequency was 20%. Mechanical ventilation in the study group was identified as a risk factor in 67.1% of cases and in the control group in 12% of cases. The type of feeding in the study group was: 39.35% of cases were on total parenteral nutrition (TPN), 30.97% parenteral nutrition and milk formula, 18.71% parenteral nutrition and maternal milk, 8.39% formula milk and only 2.58% were exclusively feed with maternal milk. The mean age at the time of diagnosis was of 10.9 days for the stage I NEC, 11.5 days for stage II and 14.3 days for stage III.

Conclusions. The only cert pathogenic factors in NEC are represented by prematurity and low birth weight. The significant number of cases in term neonates should bring the attention on the necessity of modified diagnostic criteria because under the generic term of NEC we can treat other NEC-like entities with a particular evolution pattern.

Key words: necrotizing enterocolitis, newborn, premature

Abbreviations

NEC: necrotizing enterocolitis, LBW: low birth weight, VLBW: very low birth weight, ELBW: extremely low birth weight, BW: birth weight, GA: gestational age, TPN: total parenteral nutrition, SIP: spontaneous intestinal perforation, PDA: persistence of ductus arteriosus.

Introduction

The first descriptive data suggestive for necrotizing enterocolitis (NEC) are dated in 1888 in pathological reports of neonates with intestinal perforation as a possible cause of death. The first medical report of ileal isolated perforation successfully treated belongs to Argenty in 1943.

Later in 1952, we found the first information regarding necrotizing enterocolitis in the medical literature in 2 articles published in "Z Kinderheikd" journal referring to the pathological (1), and clinical (2) characteristics of a specific form of enteritis which the authors Schmid and Quaiser are calling „Enterocolitis ulcerosa necroticans". After 1 year, the same authors have published a new article (3) in which the disease is called necrotizing enterocolitis (NEC) and the terminology is used until today. In 1964 in United States at Children Hospital from New York, Berdon published the first description of the clinical and radiological characteristic of the disease in premature newborn (4).

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In 1975 Santulli et all have published the first article reporting their experience regarding some forms of necrotizing enterocolitis in low birth weight neonates which needed aggressive surgical treatment. It is the time when it was first launched the etiopathogenic hypothesis of the disease based on the 3 components: lesions of the intestinal mucosa, alteration of the bacterian colonization and the presence of a metabolic substrate (5). An important moment in the disease description is represented by the publication of some staging criteria by Bell et all based on the clinical and radiological characteristics. This is known in the medical literature as Bell staging criteria (6). The importance of this classification is that it offers data of clinical and practical utility for an adequate therapeutic decision. In 1979 the International Register of Classification of Disease settles a code for death by necrotizing enterocolitis and in this way a more correct centralization of the epidemiological data has become possible. From that moment many scientific articles based on data review or on research activity have been published with the intention to complete the information regarding the incidence, clinical characteristics and possibilities of treatment in necrotizing enterocolitis.

Necrotizing enterocolitis affects 1 to 5% from the total neonate number in every Neonatal Intensive Care Unit and the incidence in very low birth weight (VLBW) is between 7-14% (7, 8). Published data regarding incidence of necrotizing enterocolitis vary by geographical area and the time period in which the report is done and on the other hand vary by the degree of prematurity and the birth weight (BW) of the neonate. One of the most important sources of variability of the incidence of NEC is represented by the criteria of diagnosing the disease.

NEC is a pathological entity which belongs to the premature neonate by definition but may also be encountered in term neonate. It is estimated that from the total number or NEC between 7 to 13% of cases may be encountered in term neonate with an onset of the symptoms at approximately 5 days of age and especially in the presence of some associated risk factors that can affect the mesenteric blood flow: perinatal hypoxia, congenital heart malformation, multiple births, history of umbilical artery catheterization, sepsis, polycythemia, gastroschisis (9, 10). A particular form of disease can appear in the first 2 weeks of life in extremely low birth weight (ELBW) neonate before the initiation of enteral feeding and is represented by the isolated spontaneous intestinal perforation (SIP). This entity has distinct anatomo-pathological characteristics and the prognosis of the neonates appears to be better than in the classical forms of NEC (11).

For the premature neonate the peak of incidence is situated between 2 to 3 weeks postnatal, after the immediate recovery period when the neonate is enteral feed. The sooner the enteral feed is begin the earlier the onset of NEC is. It was calculated a rate of NEC onset in weeks of life in correlation with birth weight and it was concluded that the risk period for disease onset is lower with the progression of the BW. Also the calculated risk of NEC suddenly drops when the gestational age of 35-36 weeks is reached. These observations have promoted the pathogenic theory of gastrointestinal tract maturation as a risk factor for NEC.

NEC is a multifactorial disease characteristic for premature newborns with an incidence that is in constant progression both in Romania and worldwide. In the medical literature there are still multiple controversies regarding the etiopathogeny of the disease, the role of risk factors and the clinical distinction between different forms of enterocolitis (the term of NEC covers a spectrum of disease that includes spontaneous isolated perforation and other NEC-like disease) (12,13,14).

The aim of this paper is to analyze the elements that define the epidemiological and etipathogenical profile of NEC cases diagnosed in the Regional Center of Neonatal Intensive Care Unit "Cuza Voda" Iasi and "Sf. Maria" Emergency Children Hospital Iasi and to identify the particular aspects of NEC in premature neonate cases.

Materials and methods

We carried out an analytic retrospective study that included all cases of necrotizing enterocolitis diagnosed in the Regional Center of Neonatal Intensive Care Unit "Cuza Voda" and "Sf. Maria" Emergency Children Hospital Iasi. We realized a database on the evidence of disease code that was introduced in Electronic Evidence System of the two hospitals and afterwards the information from the medical records and the operatory registers were noted. Cases were divided in two groups: study group (premature newborns) and control group (term newborns). We developed an original datasheet and the statistical analysis was performed in correlation with the following variables: gender, gestational age (GA), birth weight (BW), APGAR score, maternal and neonatal risk factors, the presence of associated anomalies, type of feeding at onset, age at onset, symptoms at onset and stage at diagnosis according to Bell criteria. The statistical analysis of all data was performed in SPSS Statistics 20 program.

Results

From January 2008 to December 2013 the general incidence of NEC was 3.32%, from a total number of 6183 neonates that were admitted in the Regional Center of Neonatal Intensive Care Unit "Cuza Voda" with a total number of 205 cases identified (155 cases at premature neonates with GA below 37 weeks and 50 cases at term neonates). The cases in premature neonates represented 75.6% from the total number of NEC diagnosed. In the statistical analysis of data the term neonate group represented the control group used to identify the particular aspects of the diagnosis and evolution of the premature babies with NEC.

The mean age of gestation in the general study group was 33 weeks. The statistical parameters of the age of gestation from the study group are presented in table 1.

Tabel 1. Statistical parameters of GA.

Mean GA	Mean -95%	Mean +95%	Std. Dev.	Min	Max	Q25	Median	Q75
33.0	32.4	33.5	4.1	24	41.0	30	33	36

The analysis of the association between NEC onset and type of delivery revealed that in premature neonates from the total number of 155 cases 102 (65.81%) were born naturally and 53 (34.19%) were born trough cesarean section. In the control group of 50 term neonates 23 cases were born naturally (46%) and 27 trough cesarean section (54%). The statistical analysis revealed that vaginal delivery is statically significant correlated with prematurity in NEC (65.81%) whereas in term neonates with NEC vaginal delivery was identified in 46% of cases (Pearson Chi-square $\chi 2=6.23$, $p=0.0125$, 95%CI).

Birth weight (BW) in the premature study group was as follows (table 2):

Tabel 2. Birth weight in NEC.

Birth Weight	< 1000g	1000-1499g	1500-2499g	>2500g	Total
Premature newborns	20	68	57	10	**155**
	12.9%	43.9%	36.8%	6.5%	
Term newborns	0	0	7	43	**50**
			14.0%	86.0%	
%	9.76%	33.17%	31.22%	25.85%	

In the premature group of NEC we found out that 12.9% of cases presented a birth weight lower than 1000g and 43.9% presented with birth weight below 1500g. In comparison with the term neonate control group with NEC there are statistically significant differences ($\chi 2=127.19$, $p<<0.01$), in this group only 14% of the neonates presented with birth weight between 1500 and 2499g.

The distribution according to Bell, Walsh and Kliegman in the group of 155 premature cases of NEC was as follows: 98 cases were diagnosed in stage I Bell (63.23%), 46 cases in stage II (29.68%) and only 11 cases were diagnosed in stage III (7.1%).

The graphic representation of NEC staging at the time of diagnosis revealed that advanced stage of disease are correlated with prematurity unlike term neonates cases in which there were no case of diagnosis of NEC in stage III Bell- Figure 1.

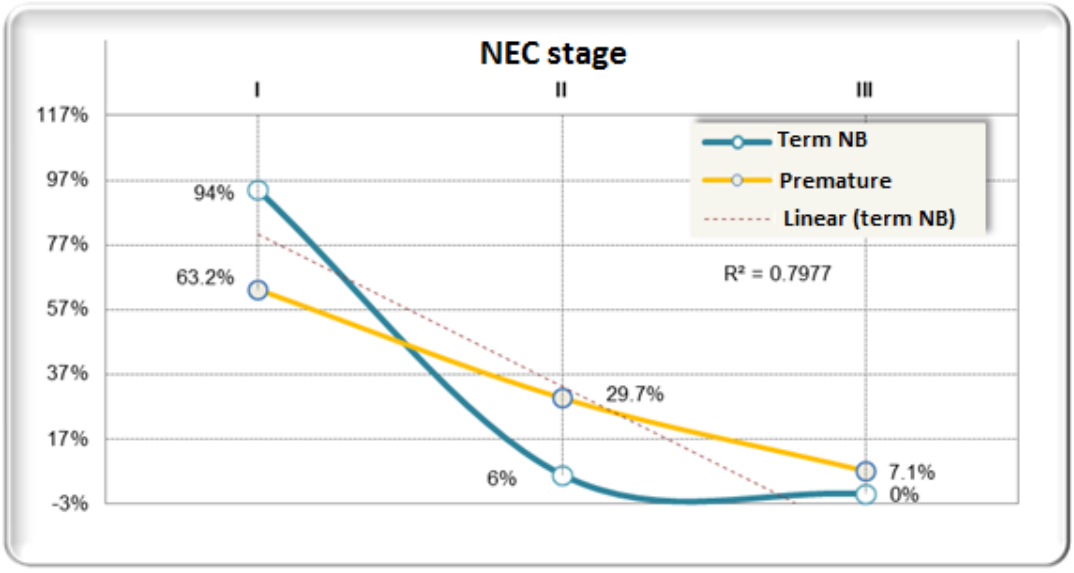

Fig. 1 Stage of NEC in premature versus term neonates.

The risk factors involved in the pathogenesis of NEC that were analyzed were the following: persistence of ductus arteriossus, perinatal asphyxia, respiratory distress, bacterial colonization, mechanical ventilation and the type of feeding at the onset of symptoms.

Persistence of ductus arteriosus (PDA) was encountered in 34 cases of premature newborns and was associated statistically significant with NEC. In the study group of premature newborns 21.9% presented PDA whereas in the control group of term neonates PDA was identified in 12% of cases, value that is statistically significant lower ($\chi2$=6.37, p=0.012, 95%CI).

Perinatal asphyxia as a risk factor for the neonates with NEC was present in 27 cases (17.42%), value that is statistically significant lower than the value in in the control group of 2% ($\chi2$=7.62, p=0.005, 95%CI).

Mild respiratory distress was identified in 51 cases (32.9%) and moderate distress in 42 cases (27.1%). Severe respiratory distress was encountered in 40% of the premature neonates with NEC and in 8% of the term cases, these data proving that there is a statistically significant correlation between NEC in premature and the severity of respiratory distress ($\chi2$=46.18, p<<0.01, 95%CI).

Bacterial colonization in cases of premature NEC was identified with a frequency of 45.2% whereas in the control group presented a lower frequency of 20% ($\chi2$=10.05, p=0.001, 95%CI). The analysis of the colonization type in premature NEC revealed the implication of Gram negative bacteria mostly Enterobacter and Klebsiella.

Mechanical ventilation in the study group was identified as a risk factor in 67.1% of cases and in the control group only in 12% of cases. The statistical analysis revealed that there is a significant correlation ($\chi2$=46.15, p<<0.01, 95%CI) between mechanical ventilation and the onset of NEC in premature newborns.

The type of feeding at the onset of symptoms in the study group was as follows: 39.35% of cases were on total parenteral nutrition (TPN), 30.97% parenteral nutrition and milk formula, 18.71% parenteral nutrition and maternal milk, 8.39% formula milk and only 2.58% were exclusively feed with maternal milk. Regarding to parenteral nutrition we did not found statistically significant differences between the study group and the control group but this differences were identified in formula feed cases with a frequency of 8.4% in premature and 34% in term neonates with NEC ($\chi2$=30.82, p<<0.01, 95%CI).

The mean age of the neonates at the time of diagnosis was of 10.9 days for the stage I NEC, 11.5 days for stage II and 14.3 days for stage III- figure 2.

We noted the fact that in cases of premature newborns the age at onset of symptoms was significantly higher comparing to the age at onset in term neonates (F=8.21, p=0.000004, 95%CI).

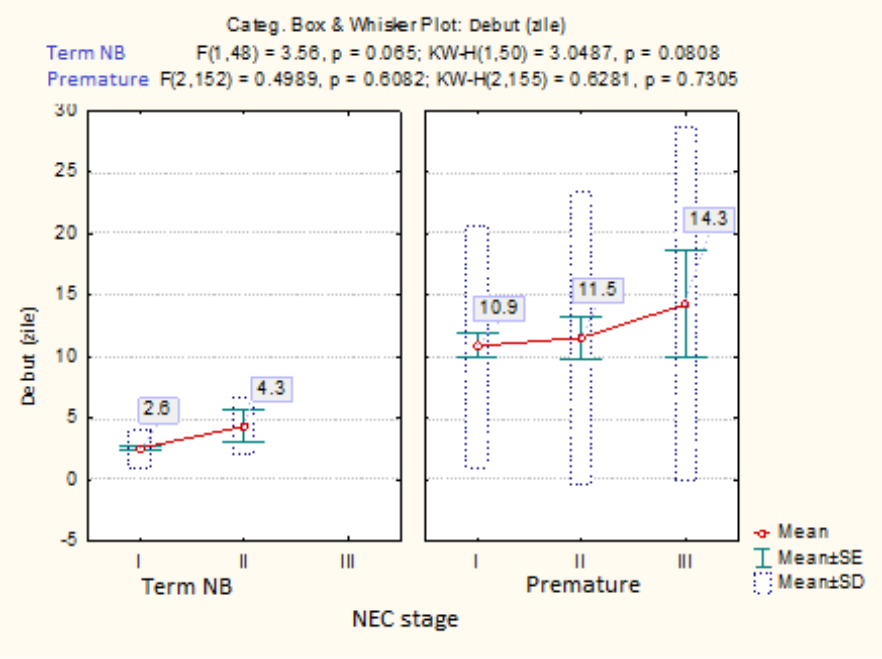

Figure 2. Statistical parameters of age at onset versus stage of NEC.

Discussion

Necrotizing enterocolitis is the number one digestive emergency encountered in premature neonate. It is universally accepted that NEC is a disease characteristic for prematurity; up to 90% from the total number of cases are diagnosed at newborns with gestational age below 36-37 weeks (15). In the study group the general incidence of NEC was 3.32% between January 2008 and December 2013. From the total number of cases 75.6% were diagnosed in premature newborns value that is below the reported number

in the medical literature of 80-90%. The high frequency of term neonates with NEC (24.4%) could be explained by a high incidence of congenital megacolon with neonatal clinical manifestation or by some possible NEC-like cases that were introduced in the study group. The risk of NEC onset is in direct relationship with the decrease of gestational age and with the very low and extremely low birth weight (12). In the study group we identified a high frequency of NEC between 28 to 30 weeks GA with 22.44% of cases diagnosed at premature less than 22 weeks of gestation. It was demonstrated a reverse correlation between the GA of the premature and the age of onset of symptoms with cases reported in the literature with onset at more than 4 weeks after birth at extremely premature. In premature with very low birth weight (VLBW< 1500g) the reported incidence of NEC is 10 to 15% (11, 12, 13, 14).

The pathogenesis of NEC remains controversial but it is universally accepted that it is a multifactorial disease. The most frequently used pathogenic theory explains the fact that NEC can occur in the event of association between the immaturity of the premature gut with the decrease of the barrier function of the mucosa, the abnormal bacterial colonization, intestinal ischemia-hypoxemia mechanism and the enteral feeding.

The factors that are influencing the bacterial colonization of the premature gut are: type of delivery (vaginal or cesarean), using of the wide spectrum antibiotics, type of feeding (maternal versus formula milk) and other factors related to the Neonatal Intensive Care Unit (Neu et al., 2008). Data from the medical literature do not show any correlations between the incidence of NEC and the demographic factors (gender, race, place of birth, age of the mother, socioeconomic status and type of delivery) but there are significant differences between the incidence of prematurity in different centers for premature based on the level of technical expertise. In the study group we did not identified significant differences in NEC cases in correlation with gender but the vaginal delivery was associated statistically significant with NEC in premature (65.81%). This finding is in contradiction with data from the medical literature where cesarean section is associated more frequent with NEC possible based on the perturbation of the normal colonization process that comes with the vaginal delivery (16).

Ischemia- hypoxemia mechanism was initially considered as the primary factor in NEC onset (Neu et al. 2008). Recent studies have shown a greater incidence of NEC in premature newborns that needed maneuvers of resuscitation at birth, mechanical ventilation in the first days after birth, in newborns with intrauterine growth restriction caused by insufficiency of the placenta or by history of abruptio placentae (Chokshi et al., 2008). In our study the severe respiratory distress was identified with a frequency of 40% in premature newborns with NEC and of 8% in term newborns with NEC, fact that proves the statistical significant correlation between the severity of distress and the EUN onset in premature ($\chi2=46.18$, $p<<0.01$, 95%CI). Regarding the mechanical ventilation we found out in our study that there is a statistical significant correlation ($\chi2=46.15$, $p<<0.01$, 95%CI) between mechanical ventilation and the premature cases with NEC, 67.1% of them being on mechanical ventilation.

The implication of Gramm negative bacteria in the disease pathogenesis is confirmed in the study group, the most frequently identified species being Klebsiella, Enterobacter and E Coli. In the medical literature a so called colonization "microbioma" of premature gut that was identified and is extremely vast but is impossible to isolate by conventional methods (16,17). The type, the volume and the moment of feeding initiation are key factors that are influencing the pathogenic mechanisms of NEC onset. Human milk contains lactobacillus and bifidobacterium species that facilitates the normal colonization process of the gut. More than 90% of the premature that will develop NEC have been fed. Regarding the type of feeding a higher incidence of NEC was found in formula milk versus maternal milk fed premature (Chokshi et al., 2008; Grave et al., 2007; Neu et al., 2008). In a randomized prospective study premature newborns that were feed with maternal milk developed NEC 6 to 10 times less than those feed exclusively with formula milk and 3 times less than those feed with formula and maternal milk (Lucas & Cole, 1990). In our study 39.5% of the premature with NEC were on TPN feeding at the time of symptoms onset, 8.39% were on formula milk and only 2.58% were exclusively on maternal milk. Statistic significant differences were noticed in cases with formula milk feeding which had a frequency of 8.4% for the premature newborns and of 34% for the term newborns ($\chi2=30.82$, $p<<0.01$, 95%CI) fact that could explain the high frequency of NEC for the term neonates group. The diagnosis of disease was established early in 92.91% of cases (stage I Bell 63.23% and stage II 29.68%), results that are consistent with the published data from the literature (Neu et al., 2008) with only 7.10% of cases that were diagnosed in advanced stage III Bell. The future finding of some clinical parameters and biochemical markers will lead to left deviation of the diagnosis curve and could create the premises of NEC diagnosis exclusively in the medical stage of disease improving the general prognosis of the affected neonates.

Conclusisons

Despite the evident improvement regarding the survival of the premature neonates, NEC remains a challenge both for the neonatologist and for the pediatric surgeon involved in diagnosing and treating this disease. In the time period 2008-2013 the incidence of NEC remained almost constant (3.32%) although the total number of the neonates admitted in Regional Center of Neonatal Intensive Care Unit "Cuza Voda" is in continuous progresion. The only cert pathogenic factors are represented by prematurity and low birth weight and this statement is confirmed by the analysis in the study group.

The presence of a significant number of cases in term neonates should bring the attention on the necessity of modified diagnostic criteria because it is possible that under the generic term of NEC to find a larger spectrum of

pathologic entities NEC-like with a particular evolution pattern.

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DISTURBANCE FACTORS IN CONDUCTING ENGINEERING STUDIES ON THE NEWBORNS' CRY, IN A HOSPITAL ENVIRONMENT

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Abstract

Engineering is becoming more and more involved in the medical practice by providing tools, techniques and working protocols that are meant to help in medical decision taking. Conducting a study in a medical environment comes with its challenges. When this study is performed by a non-medical person, outside this system, the challenge becomes even greater and has to be overcome. This paper is focused on presenting the disturbance factors that were encountered during the last 7 years of conducting a study of the newborn cry in a medical unit and the decisions taken to overcome the different obstacles. The topic of studying the cry signal generated by the newborn has been of increasing interest for both the medical and engineering researchers. Latest studies performed mostly in the last 25 years show that through feature extraction from the cry signal, relevant information can be found in order to classify different pathologies such as asphyxia, hypothyroidism, hypoxia, autism or other disorders. The study of pain cries has even a longer history, due to the fact that it clearly states an inner suffering which the newborn is vocalizing in his own language, which must be decoded and given a medical meaning. In order to perform the studies on the newborn cry, besides the cry signal, in some researches medical instruments have been also utilized in order to correlate between physiological parameters and some the cry extracted features.

Key words: disturbance factors in engineering studies, newborns' cry, spectrographic analysis, cerebral oximetry, pain cry, INVOS

Introduction

The medical field has become very interesting for engineers in the last couple of decades, which can be noticed nowdays by the presence of advanced/complex tehnique in hospitals at the hand of medical personelle. Starting with the growth of storable data which can also be processesed and interpreted with the use of computational means, the field of medical engineering has appeared around 1950 when a series of a scientific articles have been written on this topic, culminating in the '70s when this new field becomes officially recognized by the scientific communities. The complex systems that comprise the human organism, as well as the interconnections and their interdependencies, provide multiple research topics for the engineers in collaboration with the medical researchers. The field of medical engineering brings together computer science, information technology, engineering and generic technology in all the medical branches in the areas of education, research and medical practice. The evolution of this new field has been manifesting more prominently in our days when the medical world embraces these computational capabilities and utilizes them in their daily practice as a decision taking support more and more frequently [1]. As it was mentioned before, at the middle of the 20th century the first entries of informatics are reported in the medical field. These first recordings are in the field of stomatology, when despite the lack of computers, doctor Robert Ledley utilizes for the first time the computational power in his research studies, which required numerical processing of his medical data. Ledley is a pioneer of the medical informatics field, his paper dated in 1955, called „Medical progress – medical electronics" being considered a reference and a pleading for the utilization of electronics of those times in advanced medical studies. At the beginning of the '60s the first electronic recordings are reported in veterinary studies, followed at the end of the decade by human medical recordings. Nowadays, each developed country has its national centralized patient data system, which in Europe is intended to be part of a bigger system which would be comprised of the national records from all member countries [2], [3]. Besides the utilization of new techniques for keeping the recordings, the expert system, called Mycin is developed. It uses artificial intelligence in the identification of bacteria that causes severe infections like meningitis. In the context of what was presented before, engineering becomes more present each day in the medical world, especially in the hospital units.

The current study focuses on the engineering aspects that revolve around the newborns' cry. Crying is the first form of communicating by the newborn and could incorporate valuable information to direct the medical diagnosis. The cry is a complex waveform which needs dedicated tools and techniques for in depth analysis. This is where the engineering comes to help such studies, by providing both the tools and technique necessary to carry out research on these complex sound waves. The idea of studying the newborn cry in order to determine possible health problems has been started in the '60s when the first cry spectrograms have been generated.

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Current technical developments provide professional sound acquisition and feature extraction capabilities together with analysis, studies on this topic having evolved gradually, showing remarkable progress [4]-[18]. The studies performed on the newborn cry intend to find a correlation between features extracted from the recorded cry signal and certain pathologies such as: hypoxia, hearing disorder, asphyxia, autism, hypothyroidism or others.

In current medical practice, pregnancies are closely monitored and facts about the newborns health are known even before their birth, but there is the possibility of several affections which unfortunately are found only long time after birth when parents notice issues regarding the development of certain motor or mental functions or their baby's delay or inability to start expressing basic words. Suspecting a medical condition is essential in order to direct an early diagnosis and thus, being able to heal or at least stop the illnesses progression before it is too late. Most of the medical tests that can be done after birth are invasive ones and the most common consist in blood draws from the newborn. Hence, the usage of an indicator such as features from the cry can be a non-invasive method to indicate the presence of pathologies or physical state. Therefore, conducting a thorough engineering study in the Neonatology department would be more than beneficial for both the medical personnel and most important, for the newborn patient. The following paragraphs will focus on the challenges that were encountered in order to conduct such a study, named suggestively, disturbance factors and the solutions taken to overcome these.

This study of the newborn cry in order to determine patterns linking to different pathologies has been started in collaboration between engineers and the medical staff in 2008 at the Obstetrics and Gynecology Clinique "BEGA" from the Emergency County Hospital from Timisoara in the Neonatology department.

Material and Methods

In order to perform a sound analysis investigation, the equipment and protocols for performing the investigation are one of the most important elements. First tentative for recording the newborn cry implied the usage of a video recorder with an external microphone attached in order to capture the audio signal from the newborn (Figure 1). Spontaneous cries were recorder in this manner with the intent of having both facial expressions and the cry sound. The recordings were made in the hospital in different areas on random newborns. The results of this first study were not very encouraging due to a lot of noise in the audio signal. The noise over the utilizable signal was due to the presence of other audio signals over the cry, a poor recording capability and quality from the video recorder and a very difficult possibility to extract sound features like amplitude, fundamental frequency or formants from the recordings.

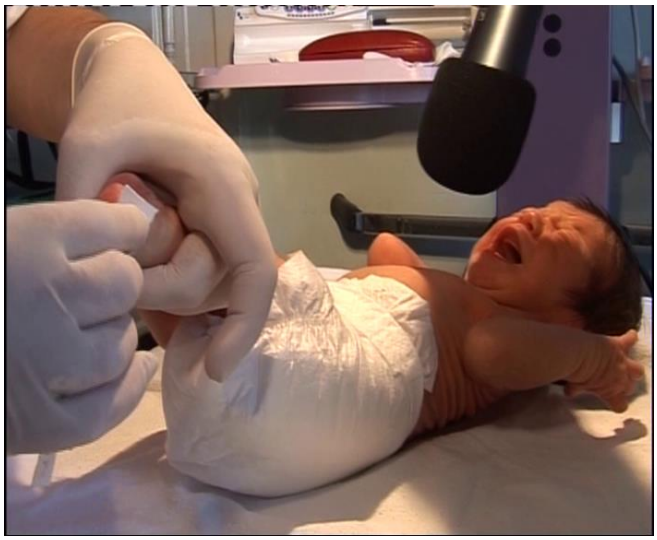


Figure 1. Video recording of a newborns cry.

In order to perform a more accurate and meaningful study of the cry, requirements were defined in order to have a system capable to overcome the difficulties resulted for the first tentative. The system needs to be comprised of a professional recording instrument that can be utilized by the medical staff which provides online and offline cry signal visualization and the most important cry features need to be extracted and visualized as well.

Having these requirements defined very clearly, the Neonat application was developed in order to be used in the Neonatology department by both medical staff and the engineers involved in the study. The Neonat application has already been presented extensively in [7]. The whole analysis system consists of a professional microphone that is connected to a laptop which has the Neonat application running on it. The cry signal captured by the microphone is analyzed in real time by the application showing a graphical representation of the sound waveform. Features from the cry signal represented by sound intensity measured in two different ways (using an emulated Volume Unit Meter and

Peak Program Meter) and sound spectrum (2D and 3D spectrograms) are both stored locally and represented visually in the application. The cry features are coupled with patient data, so that each relevant information can be accessed in a fast way by everyone using the application. Figure 2 shows a capture from the Neonat application during cry signal acquisition.

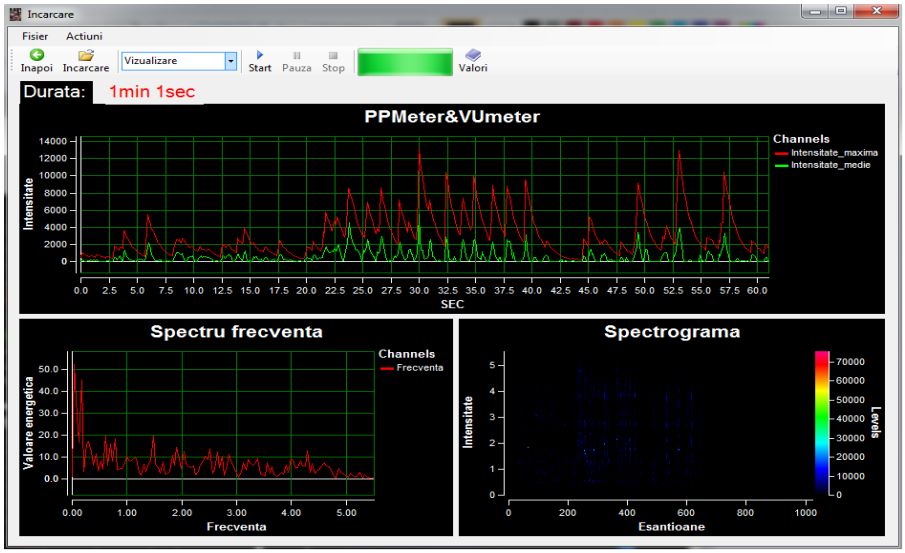


Figure 2. Capture from the Neonat application while recording.

Intensive usage of the Neonat application brought to light a series of other inconveniences when performing the study. Noisy hospital rooms, multiple users of the application and recording sessions at all times, generated the need of a recording protocol. The recording protocol was proposed in order to assure quality and repeatability of the measurements and consisted of a set of rules meant to obtain the data that needed to be gathered for the study (newborn birth data and data from the mother), equipment utilization rules (Neonat application guide and microphone set-up inside incubator) and ethical rules (consent from mother and curing doctor to perform the recording of the newborns cry). Among these rules, the equipment utilization conduit has been emphasized. Tests showed the necessity of through acquisition in terms of having a dedicated room and environment for the recording, similar recording lengths, keeping constant distance between the newborn and the microphone and in case of malfunctions of the microphone it was stated that it should be replaced with one from the same producer and with identical functional characteristics. All the rules have been detailed in one of the article presenting the Neonat application [7].

By following the created protocol, a considerable database with newborns was created in one year (approximately 200 different newborns), without needing to take out too many recordings as a result of noise, faulty handling of equipment or abnormal values of sound extracted features. With such a database a Data Mining study could be performed in order to make a classification between different categories of newborns that were considered. The results of this study have been presented in [19].

The focus of the work was shifted then in determining patterns in the newborn cry that can be linked to physiological measurements such as the cerebral oxygenation. Such correlations have been studied and are still of interest to different interdisciplinary groups where medical personnel works together with sound technicians or engineers to determine the impact brought to the cry signal by heart rate fluctuations, peripheral or cerebral blood oxygenation among others [21], [22].

The study performed by our group consisted in the utilization of several equipment for the cry signal acquisition, real time visualization and post processing together with the measuring of the cerebral blood oxygenation during lab draws. A professional acquisition tool, the Olympus LS-100 PCM Multi Track Recorder was brought into the study in order to have a very good quality recording and to be able to do precise post processing and analysis of the cry signal. In order to determine the cerebral blood oxygenation the oximeter INVOS 5100C has been used. This medical equipment helps to determine in a non-invasive way the ischemic risk (the local deficit of blood) at the brain level or vital organs by measuring the hemoglobin level right under its sensors on the monitored area of the scalp (in this study). The measured parameter is represented by the regional hemoglobin oxygen saturation (rSO2) which is the value at tissue level of the oxygen from the hemoglobin which is left after tissue irrigation [20]. The main goal of the study that was performed was to follow the modification of the blood saturation at cerebral level when pain is present, in this case when the medical personnel performs blood draws from the newborn and correlating this information with features extracted from the pain cry using the Neonat application. The cry signal was visualized in real

time with the Neonat application and acquired for post processing with the Olympus PCM recording device.

This new direction of the study required more people to be present during a recording: a nurse for performing the blood draw, an operator for the Neonat application, someone to start/stop the Olympus recording device and give the signal for the blood draw sting and an operator for the NIRS equipment. Having this number of people involved at the same time requires precise timing and coordination between all the team members, otherwise the results would be impossible to interpret. The information collected by the INVOS tool about the rSO2 parameter is localized, in real time and continuous. Therefore it allows the possibility to correlate its values with features from the cry signal which are as well in real time and continuous. The problem of the data coming from the cerebral oximeter is represented by the frequency of the measurement, which is fixed at 5 seconds. Therefore the need for one of the team members to give signals at each of the important events during the procedure (starting the recording, setting the cerebral oxygenation parameter baseline, start of the procedure, end of the procedure, stopping the recording) which need to be known and given a time stamp.

Given all the equipment and techniques tried so far in the study of the newborn cry, it can be concluded that in terms of material and methods it is very important to have a protocol to follow during procedures, which in most of the cases was the result of several faulty tentative. The following paragraphs which contain the results will highlight these aspects concerning wrongful procedures and the correction of these.

Results

The first cry acquisition system that was tried out, comprised of the video recorder and the external microphone connect to it, was analyzed in terms of the recorded cry signal is shown in the form of a waveform for one of the newborns is Figure 3. This waveform which was generated was the result of using external sound analysis software and is very affected by noise coming from the ambient and internal equipment noise as well. In order to be able to get useful information from this, filters can be applied. The only problem with applying a low pass filter for instance is represented by a minimal threshold value that needs to be set for the filter, in order to allow values only above that value to pass the filter. Without having a past experience with the newborn cry, setting this lower threshold presented the risk of leaving out values that are not part of the noise, but information from the cry itself. Similar thoughts are available when applying a high pass filter or a band pass filter, namely the possibility of losing features from the cry itself in the tentative of cleaning the noise that is over it. Each of the recordings made in this manner have similar waveforms, and the need of filtering is available there as well.

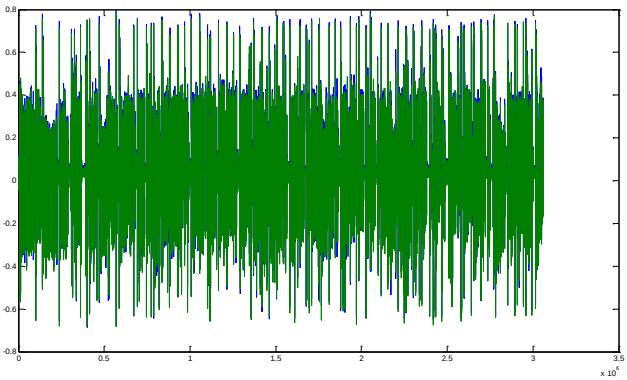


Figure 3. Waveform of a cry recorded with the video camera.

The Neonat software was created for the purpose of having a dedicated tool that can allow both the acquisition and analysis of the cry signal. The software allows a fast configuration for the acquired sound (selecting amplitude representation interval, filters and their parameters, sampling rate, Fast Fourier Transform detailed configuration and other parameters considered useful for the study) and visualization possibilities (2D and 3D spectrogram for data chunks or for the whole cry signal, sound intensity, Volume Unit Meter or Peak Program Meter measurements). This way, many of the disturbance factors can be eliminated and the acquired information becomes more reliable. The screen capture of the on line sound acquisition was presented in Figure 2.

Developments have been obtained and presented in articles of the authors [7], [19] by using this special developed software, Neonat. First studies were conducted in order to determine the protocol (which was mentioned in the previous section) for performing the later on experiments, which consisted in a Data Mining analysis of several new born groups with similar pathologies with the intent of making a classifications between healthy newborns and each of these groups. The results of this study showed a very good classification capability of the tool Weka (which was incorporated in the application) when searching differences

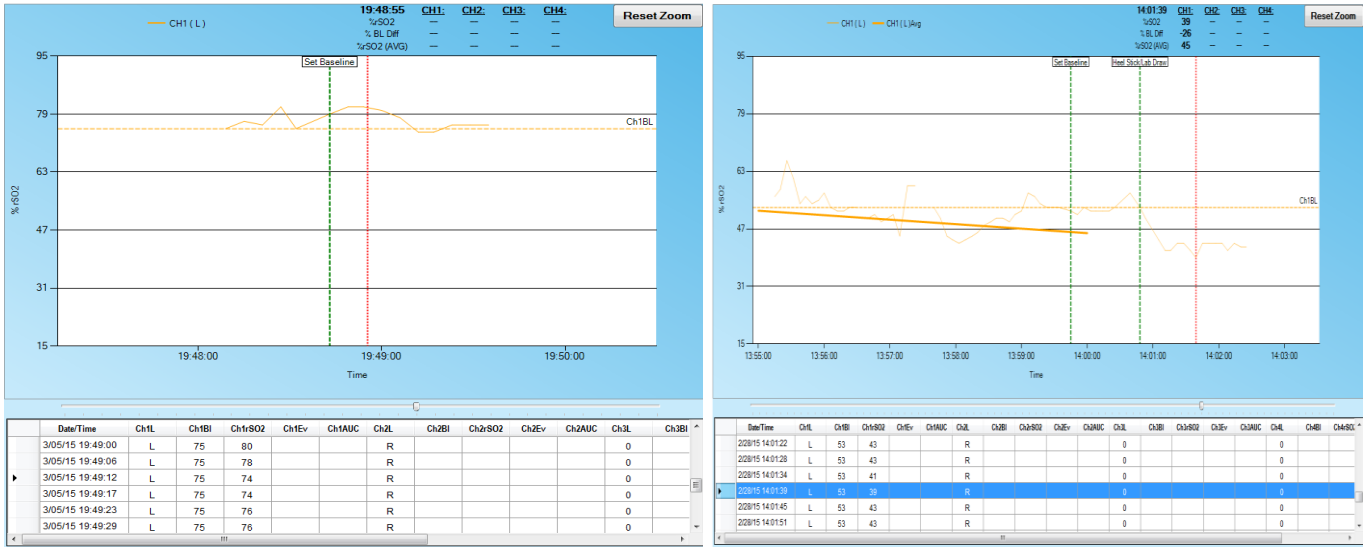
between the witness group (healthy newborns) and a group of premature newborns (gestation age < 38 weeks), a group comprised of newborns with respiratory problems and a third cluster of newborns with Apgar score below 7 which were born on time but diagnosed with severe illnesses like neurological suffering.

The results obtained in these first steps, determined the new approach on the cry analysis. As it was mentioned before, the focus was directed towards determining patterns in the cry that could be linked to physical parameters. In the study conducted with the INVOS cerebral oximeter and the auxiliary recording instrument, the Olympus PCM recorder the synchronization between the team members was a big obstacle that needed to be handled. The protocol for this study was created to assure that the information about the rSO2 was mapped correctly on the cry signal in different important moments: baseline setting, nurse starting the blood draw procedure or the blood draw end point. Nevertheless, after having all tasks synchronized and results starting to show there have been noticed several cases when the behavior and evolution of the cerebral oxygenation was not the foreseen one. In these situations, the expected decrease of the oxygenation parameter was not very visible or it presented as an increase (Figure 4 a)). This result was possible when the needle sting or the blood draw did not affect in any way the newborn. There were situations in which all these invasive actions did not generate an expected cry of the newborn and an increase in the saturation could be seen. Two main factors can lead to such a situation:

- the nurse doing the procedure can puncture the vein where the collecting is done, immediately without inducing any pain;
- the newborns pain acceptance level is so high, that it needs a more powerful action to inflict this pain.

Although these situations can be seen very fortunate from the patient caring point of view, in terms of the study these are disturbance factors that make such cases unusable for the study.

In Figure 4 b) is an example from the INVOS software, showing the variation of a newborns' cerebral oxygenation. This example shows a very big decrease in saturation which can be very dangerous for the newborns' state. Such a big decrease can cause brain lesions and is a very unfortunate situation when no monitoring is performed. Since cerebral oxygenation monitoring is not usually performed given the costs that it implies, and without an indication of its necessity, cry analysis can be a very viable alternative if it can give an indication about the cerebral oxygenation level, for instance.



a) b)

Figure 4. Screen captures from the INVOS software.

The choice of this example shown in Figure 4 b) is due to the developments of this newborns' case. Such a big decrease in the saturation, below the value of 40% and a high dominant frequency that was noticed in the cry spectrogram of the word following the puncture, lead to further investigations that discovered a neurological suffering of this newborn. Although this was not the goal of the study, the result was very encouraging for the overall purpose of the newborn cry signal study in order to determine patterns for different pathologies. Although for the other cases such a situation like the one presented was not as clearly highlighted, there were similarities regarding the high decrease in the rSO2 value and dominant frequencies above 1 kHz. Such a high dominant frequency even for a pain cry with no energy components on lover frequencies (400Hz-600Hz) looks to be consistent with the saturation decrease.

Conclusion

The ongoing study of the newborns' cry analysis presents itself with a lot of challenges. In this paper were highlighted a couple of the disturbance factors that have been noticed and overcome in the last 7 years of studies of this topic. The study has gone through different stages, each of them highlighting problems that can occur and which need to be overcome.

Beginning of the study showed the necessity of a sound proof room and the need of a dedicated equipment coupled with a software tool in order to make custom settings to be able to rely on the output results. In this context, the Neonat software was created and the recordings have been taking place in dedicated hospital rooms inside incubators.

When having dedicated software which is easy to use by the medical personal it is necessary to create a procedure protocol in order to offer the same conditions to all the subjects present in the study. A protocol was created as a result of past experience and the results became reliable and first conclusions were drawn by using Data Mining techniques to perform a classification of the newborns present in the study.

Such a long term study can have multiple developments in time. The idea of having other equipment to conduct other type of studies is something that is meant to happen. This will generate other types of disturbances in the study, like the problem of having to synchronize work of 4 team members with 4 different tasks on different equipment or the different nurses participating in the study, with different abilities to puncture a vein that can lead to different reactions from the newborns investigated.

Overall, the study has shown so far very promising results that were obtained when dealing with disturbances from the engineering point of view, namely: dedicated tools, well defined work protocols and synchronization between tasks in order to have reproducible and reliable outcomes.

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THE INTENSIVE CARE COURSE WITH FLUIDS AND ELECTROLYTES IN NEWBORN FOR PREVENTING COMPLICATIONS

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Abstract

Fluids and electrolytes therapy is one of the most important and useful methods
applied in the pathology of newborns and of low birth weight infants particularly.

Total and extra-cellular water in the organism, expressed as percentage of body
weight, gradually decrease as the gestational age increases.

These dynamic changes in the quantity of water in the organism are of practical importance, as the distribution of electrolytes or drugs fluctuates along with the maturity stage of the child. After birth, administration of fluids will take into consideration: the changes in body composition; nutrition changes; the changes in the development of renal function, and the changes due to the environment and to the water requi red for growth.

In this paper, we present in detail all these aspects. Finally, we approach some of the major problems of fluid therapy: extremely low birth weight infant; the newborn with: perinatal asphyxia, respiratory distress syndrome, acute renal failure; bronhopulmonary dysplasia; children with congenital heart disease; preterm newborns with patent arterial duct; gastrointestinal fluid losses; gastrointestinal tract obstructions requiring surgery.

Key words: newborn, dehydratation, fluids, electrolytes

Introduction

The abrupt exclusive nutrient supply to the fetus through maternal placenta during birth, is a challenge for neonatal physiology, especially the premature onset of extrauterine life (1).

The use of fluid and electrolyte management is one of the most difficult aspects of the neonatal care of premature infants. Understanding the processes of the neonatal adaptation to the extrauterine life and how the transition affects premature immaturity is based on the management processes postnatal electrolyte rebalancing (2).

Often this group of infants, the enteral nutrition is impossible, due to the immaturity of the digestive tract; the total parenteral nutrition in the management accounting nutrients needed for growth and development only intravenously. Installing venous lines for the total parenteral nutrition involves skills training health personnel, strict hygiene conditions (aseptic and local antisepsis) and is often marked by complications (pain, skin lesions, port of entry for pathogens).

The total parenteral nutrition comprising macronutrients (source of glucose solutions of carbohydrates, solutions of amino acids of the protein source, the fat source solutions fat), micronutrients (vitamins, minerals, metals). The partial parenteral nutrition is the intravenous administration of nutrients and suboptimal quantity, enteral (12).

The parenteral nutrition is carried out individually, depending largely on the age and weight of the newborn. Failure enteral feeding (due to immaturity or suffering) requires the introduction of total parenteral nutrition in a few clear categories newborns:

a) more than 30 weeks gestational age and / or weight below 1000g;

b) over 30 weeks of gestation with neonatal pathology that makes it impossible to achieve optimal nutritional potential;

c) intrauterine growth restriction;

d) digestive inflammatory disease (necrotizing enterocolitis);

e) metabolism in severe overload: congestive heart failure, acute renal failure;

f) congenital anomalies or gastrointestinal surgery: gastroschisis, omphalocele, intestinal atresia, intestinal volvulus, intestinal malrotation, intestinal obstruction, short bowel syndrome, meconium ileus, etc.

The study by Min Young Kim and his colleagues, Gachon University of Korea, in a group of 258 premature periada 2004-2007, comes to reveal metabolic changes during the first period of life, the extreme small premature infants (ELBW).

Their research results show that in the first 72 hours of life of extremely small premature infants often install hyperkalaemia non-oliguric a great threat to the lives of children and a challenge for neonatologists.

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The hyperkalemia can cause arrhythmias, intracerebral hemorrhage and periventricular leukomalacia, and sudden neonatal death. Conventional therapeutic interventions aimed at redistributing serum potassium (or sodium bicarbonate injection of insulin and glucose) increased removal of potassium in the body (diuretics, ion exchange resins, exchange transfusion, salbutamol or albuterol) or the treatment of hyperkalemia caused by arrhythmias may calcium (7).

A study conducted by Daniela Jacob and his collaborators in the Department Neonatal TI of Maternity Bega in 2012 and 2013, showed a prevalence of metabolic disorders 76.1% among extreme low birthweight preterms (ELBW). The study group consists of 46 extremely low birthweight infants with birth weight less than 1000 g and gestational age 24-30 weeks. All these premature conducted fluid and electrolyte therapy.

The cord transection disrupt the supply of nutrients to the newborn; this has a strong impact on prematurity in the first 24-72 hours of life; with hyperkalemia, hypocalcemia neonatal install. Using postnatal intravenous calcium compensate these losses, counters hyperkalaemia and antiarrhythmic effect (7).

THE WATHER BODY COMPOSITION NEWBORN

The body fluid composition varies inversely with gestational age; the body preterm gestational age of 23 weeks, with 90% water (60% extracellular and 40% intracellular). Healthy newborn body contains 75-80% water time (40% extracellular and 60% intracellular). Physiological decrease in the first week of life varies by gestational age: preterm lose 10-15% of birth weight and term newborn 5-10% (3).

THE FLUID THERAPY IN PRETERM INFANTS

Setting caloric needs (although there standard recommendations for energy needs) is the first step in the initiation of total parenteral nutrition.The nutrient management with 24 to 25 kcal/kg/day, immediately after birth, newborns with 24-40 weeks of gestation, provides energy balance. Energy requirements for providing bas 40 kcal/kg/day (3).

In order to ensure an increase in the daily 15 g/kg, in addition to the basal metabolism is needed 45-67 kcal/kg/day (3).

The heat distribution is as follows: 60-65% carbohydrate, 10-15% protein and 30-35% lipids, and the ratio of protein /energy must be 3-4 g /100 kcal.

In the total parenteral nutrition is necessary to achieve balance between fluid intake depending on the needs of premature loss of fluid (urine, stool, loss and loss insensitive pathological) and distribution of fluids in the body. On the first day of life will be given a quantity of liquid individualized 60-80 ml / kg / day and gradually increase depending on pathology, diuresis, level of hydration. At the end of the first week of life will ensure endovenous 150 ml / kg / day of fluid; this need is standardized tables hydric needs of infants, being present in all sections of neonatology.

The protein needs of premature depends on gestational age and birth weight, growth and catabolism is high. To ensure 15% of the energy needs of premature infants is necessary to introduce amino acid infusions, often from the first day of life, with 1-1.5 g/ kg/day initially; increase the intake of 1 g / kg / day up to a maximum of 3-3.5 g/kg/day for losses urinary, digestive and skin and provide age-appropriate growth.

The aminoacid solution will contain essential aminoacids (phenylalanine, histidine, leucine, isoleucine, lysine, methionine, threonine, valine) and the conditionally essential (arginine, cysteine, glycine, glutamine, proline, taurine, tyrosine).

The carbohydrate requirement of total parenteral nutrition is provided by glucose; glucose solutions also provide most of the energy substrate prematurely with cerebral role in metabilism. The very small infants (VLBW) and extremely low (ELBW) and in patients with respiratory distress or hypothermia need glucose soon after birth. Administer glucose solution (10% or 5%) with 4.6 mg/kg/min in preterm VLBW and 10.8 ml/kg/min in preterm ELBW providing 40-50 kcal/kg/day. After the normalization of the blood glucose, increase the glucose infusion rate to 0.5-1 mg/kg/min, up to a maximum of 12 to 13 mg/kg/ min (12). Detailed data are presented in the following table.

Table I. Macronutrients intake in the total parenteral nutrition of the newborn: Guidelines for initial therapy and supportive (after Wessel J, Kocoshis S. Nutritional Management of Infants with Short Bowel Syndrome. Semin Perinatol. 2007)

		Initial	Usually	Total
Premature < 32 weeks < 1000 grams	Dextrose	4 – 6 mg/kg/min	1 – 2 mg/kg/min	≤ 12 mg/kg/min
	Aminoacids	3 – 3.5 g/kg/d	0.5 - 1g/kg/d	4 g/kg/d
	Lipids	1 g/kg/d	0.5 - 1g/kg/d	3-3.5 g/kg/d
	Non-proteic calories	40 -50 kcal/kg/d	60 – 70 kcal/kg/d	85 – 95 kcal/kg/d
	Total Calories	50 – 60 kcal/kg/d	70 – 80 kcal/kg/d	90-100 kcal/kg/d

Premature < 32 – 36 weeks, > 1000 grams	Dextrose	4 – 6 mg/kg/min	1 – 2 mg/kg/min	≤ 12 mg/kg/min
	Aminoacids	3 – 3.5 g/kg/d		3.5 g/kg/d
	Lipids	1 g/kg/d	0.5 - 1g/kg/d	3 g/kg/d
	Non-proteic Calories	40 -50 kcal/kg/d	60 – 70 kcal/kg/d	85 – 95 kcal/kg/d
	Total Calories	50 – 60 kcal/kg/d	70 – 80 kcal/kg/d	90-100 kcal/kg/d
Newborn to term > 37 weeks	Dextrose	6 – 8 mg/kg/min	2 – 3 mg/kg/min	≤ 12 mg/kg/min
	Aminoacids	2 – 3 g/kg/d	0.5 - 1g/kg/d	2.5 – 3 g/kg/d
	Lipids	2 g/kg/d	0.5 - 1g/kg/d	2.5 – 3 g/kg/d
	Ca	40 – 50 kcal/kg/d	50 – 60 kcal/kg/d	70 – 80 kcal/kg/d
	Total Calories	50 – 60 kcal/kg/d	60 – 70 kcal/kg/d	80 – 90 kcal/kg/d

Necessary minerals, vitamins and trace elements will ensure the appropriate intravenous solutions, depending on the daily needs of specific pathology and daily losses of prematurity.

It is not generally necessary, to add Na, K, and Cl in the first 24 hours; if the diuresis is normal after the first day of the life, the need for sodium is 1-3 mEq / kg / day and potassium needs 1-2 mEq / kg / day (9).

The daily requirement of minerals is necessary chlorine 2-3 mEq / kg / day calcium requirement 150-200 mg / kg / day magnesium needs 15-25 mg / kg / day and phosphorus needs 20 to 25 mg / kg / day (8).

Daily vitamins are: vitamin A 1640 IU/kg/day, vitamin D 160UI/kg/day, Vitamin E 2.8 IU/kg/day, Vitamin K 80 mcg/kg/day, vitamin B6 180 mcg/kg/day, vitamin B12 0.3 mcg/ kg/day, vitamin C 25 mg/kg/day, folic acid 56 mcg/kg/day, biotin 6 mcg/kg/day, niacin 6.8 mg/kg/day thiamine 350 mcg/kg/day, riboflavin 150 mcg/kg/day (6).

The daily requirement of trace elements in premature is Zinc 400 mcg/kg/day, Cooper 20 mcg/kg/day, Selenium 2 mcg/kg/day, Chrome 0.2 mcg/kg/day, Manganese 1 mcg/kg/day, molybdenum 0.25 mcg/kg/day, Iodine 1 mcg/kg/day (12).

The therapy with fluids and electrolytes in the neonatal period is not without complications:

a) relating to the catheter: sepsis, extravasation of solutions, thrombosis, obstruction of the catheter;

b) related to treatment: hypo / hyperglycemia, azotemia, metabolic acidosis, cholestasis, hypertriglyceridemia, fluid and electrolyte disorders, liver problems, vitamin deficiencies and ologoelemente and osteopenia.

In the neonatal sepsis in premature infants and the court will begin fluid therapy with lower doses of aminoacids, the maximum dose of 2.5 g / kg / day protein (major risk of cholestasis).

The administration of glucose solutions in excess increases the basal metabolism, the fat deposition, the cholestasis, the hepatic steatosis and the overeating. ELBW infants often show hyperglycemia and therefore will ensure a glucose infusion rate below 4 mg/kg/day (7).

The routine use of lipid solutions is not supported in VLBW infants with severe and mechanically ventilated because of possible complications: fat intolerance, adverse effects on lung function, risk of chronic lung disease, interference in bilirubin binding to albumin, impaired function immunological and platelets. The rate of injection is using a solution of lipid in 0.5 g / kg / hr and slowly increases up to 3 g / kg / day.

After the stage of the total parenteral nutrition, the enteral nutrition is minimum phase (priming), and the enteral feeding of premature by digestive tolerance.

PREMATURE CATEGORIES REQUIRING A SPECIAL FLUIDS AND ELECTROLYTES THERAPY

Infants with the intrauterine growth restriction and hypoglycemia will be admitted to Neonatal Intensive Care Unit (NICU) and will be infused with 10% glucose initially 60-80 ml /kg/day (8.4 mg/kg/min); in severe hypoglycemia (blood glucose below 20 to 25 mg/dl) is given boluses of 2 ml/kg 10% glucose, then endovenos infusion 6-8 mg/kg/min, with monitoring of blood glucose in 30-60 minutes, to obtain values normal. The protein intake in these premature infants is 3 g/kg/day and fat intake of 0.5-1 g/kg/day (12).

Infants with lactose intolerance often require parenteral nutrition, achieving rebalancing electrolyte, and the introduction of enteral nutrition in parallel with increased digestive tolerance (11).

Mechanically ventilated infants requiring parenteral nutrition early in the first hour of life, and a necessary caloric 90-100 kcal / kg / day. Hussein and Rosenkrantz have conducted a review of studies casuistry extremely small preterm who received surfactant therapy with fluids and electrolytes: in infants with a gestational age of 22 weeks survived only 4%, 21% with 23 weeks of gestation and 46% with 26 weeks of gestation (5).

The cyanotic heart malformation preterm often develop congestive heart failure and pulmonary hypertension, with an impact on growth and development. Ensure caloric intake by 50% higher than that of healthy children (5).

A group of researchers at Rhode Island Hospital and Brown University School of Medicine studied fluid therapy in a group of 170 premature infants with birth weight of 751-2000 g and patent ductus arteriosus divided into two study groups: first group was made fluid restriction and the

second group were given the excess fluid (a 20 ml / kg / day versus daily fluid requirement for gestational age). The results are clear: 35 of the 85 preterm excess liquid had a heart murmur, marking the presence of a ductus arteriosus, and 11 of the 35 preterm developed congestive heart failure; only 9 of the 85 preterm fluid restriction had systolic susflu the ductus arteriosus and 2 of the 9 had premature cardiac insufficiency. They turned and necrotizing enterocolitis were more common in the group that received excess fluid (2).

Infants with metabolic disorders (abnormal carbohydrate metabolism, protein, urea cycle defects, abnormalities in fatty acid oxidation, organic acidemia, peroxisome and lactic etc.) requires early diagnosis and appropriate treatment. It requires dietary restriction metabolites incriminated in the disease, and supplementing deficient substances.

The acute and chronic renal insufficiency often marks the beginning stage of life prematurely. The appropriate caloric intake should be provided, taking into account the loss of urinary and gastro-intestinal organic and insensible losses (10).

The hepatic cholestasis, hepatic or extrahepatic obstruction caused by, associated with deficiencies in the drainage of the bile from the gall bladder. It will eliminate the fat and chromium solutions of intravenous fluid therapy (12).

Conclusions

The cord transection disrupt the maternal-fetal blood flow; at this point stop and newborn supplies nutrients. Most affected by this mechanism are the premature, which, depending on gestational age and birth weight often requires intensive care with fluids and electrolytes, nutrients necessary to ensure normal growth and development.

Needs of macronutrients (proteins, carbohydrates, lipids) and micronutrients (electrolytes, salts, vitamins, trace elements) will be provided about vein; will perform parenteral nutrition central venous or peripheral.

Often marked by intensive neonatal complications (lesions at the injection site, systemic disease). The specific neonatal pathology (especially complications of prematurity) requires prudent management and therapeutic nutrients often as necessary restrictions or liquid nutritional supplements.

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PARTICULARITIES OF INFECTION IN CACHECTIC CHILDREN

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Abstract

Infections are frequent in childhood, especially in the presence of malnutrition. The etiology of poor state of nutrition can be: incorrect feeding, congenital defects, frequent infections, improper care or a mix of the previous situations.We can diagnose cachexy in children whose BMI is <5 percentiles and under 3-rd negative deviation.

Authors present four cachectic patients: two children suferring of trisomy 21, who had associated each one heart malformation: first, a boy, N.S., aged 7 had Fallot tetralogy and bacterial endocarditis; second, a girl, P.S, 4 years aged had ventricular septal defect and acute interstitial pneumonia. The third cachectic patient was a girl aged 8, D.C. with Seckel syndrome, admitted for staphylococcal pneumonia; the fourth is a 8 years girl P.ER with spastic tetraparesis, microcefaly, diagnosed with severe sepsis. Only the boy suffering of endocarditis, evoluated to MODS and death; the three girls were discharged healed. Trisomy 21 caused immunodeficiency and cachexy also permitted severe infections. Their poor state of nutrition had a combinated etiology: congenital defects, improper diet, recurrent infections, inadequate care (two patients lived in orphanage, two girls had only mother). Congenital heart defects could been complicated to endocarditis. In thin children, with birth malformations, pneumonia is frequent. Cachexy in malformed children is an important cause of immunodeficiency which leads to severe, sometimes letal infections. Infections produce denutrition and cachexy promotes severe sepsis, especially in parentless children.

Key words: cachexy, severe sepsis, infection, child.

Background

The World Health Organization estimates that malnutri tion is incriminated for 54 percent of child mortality worldwide, for death of about 1 million children. Even mild degrees of malnutrition double the risk of mortality from respiratory and digestive diseases. This risk is greatly increased in the most severe cases of malnutrition such as cachectic children. According to a 2008 review (15), the authors estimated that 178 million children under age 5 were stunted, most of them living in Africa. A 2008 review (15.) of malnutrition found that about 55 million children suffered of severe acute malnutrition, including 19 million who were cachectic. Pediatric cachexy or wasting syndrome is loss of weight, muscle atrophy, fatigue, weakness, and significant decrease of appetite in children, despite of their normal birth weight (12). A definition of cachexia is the loss of body mass that cannot be reversed nutritionally: when it occurs in preschoolar and schoolar patients, frequently they had a relative normal weight in their first childhood (according their medical history)(15). Even if the affected pediatric patient eats more calories, lean body mass will be lost, indicating a primary pathology is in place(12). The etiology of poor state of nutrition in children can be: incorrect or insufficient feeding, frequent infections, congenital defects, improper care or a combination of the previous situations. There remain three commonly used measures for detecting malnutrition in children: stunting, (extremely low height for age, under 80 percent of normal), underweight (extremely low weight for age, under 60 percent of normal) and wasting (extremely low weight for height, under 70 percent, NI<0.7)(12). We can diagnose cachexy in children whose BMI is <5 percentiles and under 3^{-rd} negative deviation (according to WHO 2007 children growth)(13). These measures of malnutrition are interrelated, but studies for the World Bank found that only 9 percent of children of the world exhibit stunting, underweight and wasting. Measurements of children's growth provide the key information for the presence of malnutrition, but weight and height (measurements) alone can lead to failure in recognizing kwashiorkor and to an underestimation of the severity of malnutrition in children.

Infectious diseases, especially respiratory and digestive infections are often found in pediatric population. Sepsis is defined like a systemic inflammatory response syndrome (SIRS) induced by an infection (1,2,3,4). Severe sepsis is sepsis associated to blood hypotension or with hyperglicemia, with hypoperfusion and a single organ damage (5,6). Infectious MODS suppose sepsis with dysfunction of at least two organs (5,7,10). Septic shock means sepsis with hypotension longer than an hour despite a proper fluid rebalancing (9,10,11).

Matherial and method

We conducted a study about four cachectic patients, including three girls who were directly supervised by the authors of the paper.

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We used clinical observation worksheets, during their hospitalization in Pediatrics Clinic, Emergency Hospital of Craiova, the length period of study being since march 2013 to april 2014.

Subjects were: two children with trisomy 21, both of them having cardiac malformation and associated medical conditions: the first one, a boy, N.S., aged 7 had Fallot tetralogy and congenital solitary kidney; the second one, a girl, P.S, 48 months aged, had ventricular septal defect, congenital duodenal stenosis and recurrent interstitial pneumonia. Children suffered of L.Down disease lived in orphanage. The third cachectic patient was a girl aged 8, D.C. with Seckel syndrome, admitted for febrile seizures, hypotonia and coma; the fourth was a 9 years girl P.E.R. with spastic tetraparesis, microcephaly, diagnosed with severe sepsis. The last two girls were grown of their alone mothers. We analysed their diagnoses, laboratory findings and the evolution of infection in the same case.

Results

Case 1

The boy patient **N.S**., 7 years and 9 months age, W= 12 Kg, was admitted in First Pediatrics Clinic of Craiova in 27-03-2014 for high fever, hyporesponsiveness, hypotonia, generalized cyanosis, in a child suffering from tetralogy Fallot associated with 21 trisomy. Based on medical history, on clinical examination at admission (which revealed: orthopnea, hypotonia, generalized cyanosis, breathlessness, tachycardia, 4/6 systolic ejection murmur, late capillary refill time, low blood pression, hyporesponsiveness to verbal stimuli, motor deficit on the right side of the body, and clinical appearance of L. Down disease) and confirmed by laboratory findings (WBC= 13700/mmc, PMN=81%, Ly=15%, Mo=4%; Hb=19,8g%, PLT=87000/ml; INR=1,22; pH=7,25; pO_2=51,4mmHg; pCO_2=50,4mmHg; ESR=1mm at 1h/3mm at 2h; CRP=48 mg/l; chest-X-ray revealed heart „en sabot"; cardiac ultrasound: „Ventricular septal defect, aorta „riding" the interventricular septum; suggestive formation like vegetation on tricuspid valve"; abdomino-pelvic ultrasound: „single kidney"; cranial tomography: „Recently cerebral hemorrhagic stroke on cerebral trunk") the following diagnoses were noted: „Severe sepsis. Unknown etiology endocarditis. Cerebral hemorrhagic stroke on cerebral trunk. 21 Trisomy. Cachexy." Despite of treatment (hydroelectrolyte and metabolic rebalance, strong antibiotherapy) the patient died at the 8th day after admission, but histopathological examination confirmed the clinical diagnosis.

Case 2

Girl patient **P.S**. (figure 1) 4 years age, weighting 10 kg (at first admission), then has weakened 1 kg, with ventricular septal defect in the context of trisomy 21, had in her past medical history a surgical intervention for duodenal stenosis, several lung infections.

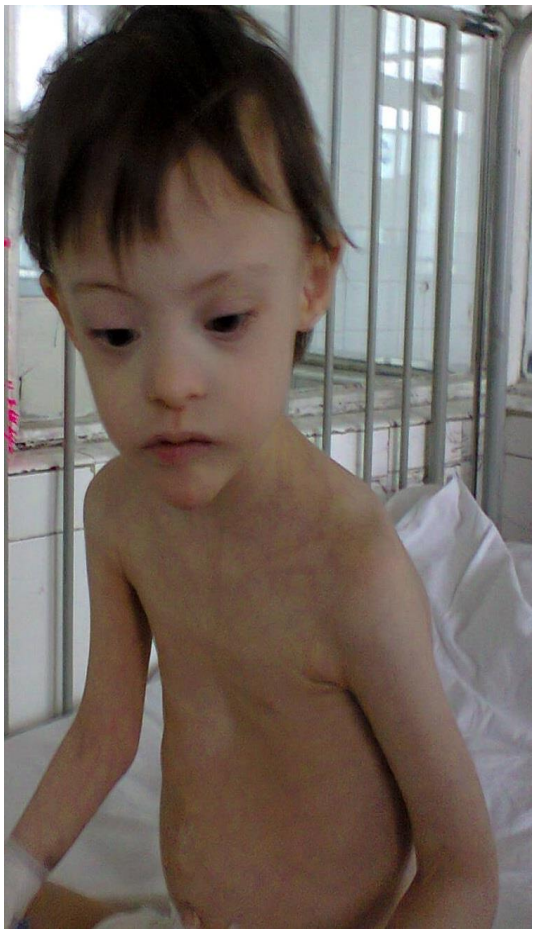
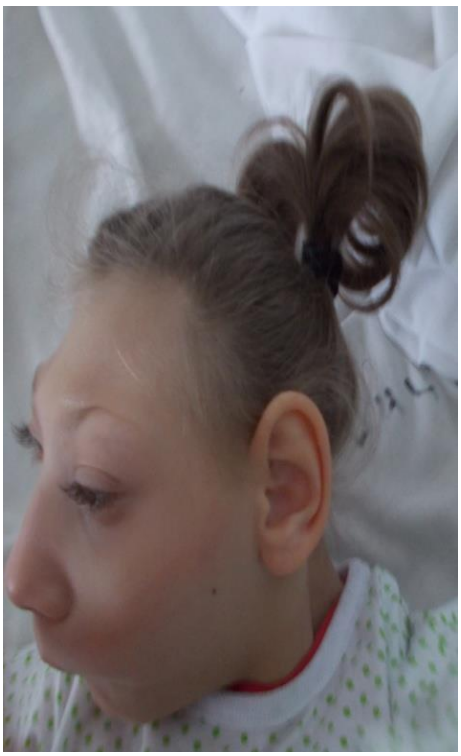


Figure 1: PS-from orphanage.

Based on clinical examination at second admission in 2014 (which revealed: W=9000g, H=83 cm, pale skin, lean tissue absence; peripheral temperature =37,8°C, cough, dyspnoea, tachypnea, bilateral bronchial and crackling rales, 3/6 systolic ejection murmur audible anterior and posterior, and clinical appearance of L. Down disease), according to laboratory findings (Hb=8,8g/dl, WBC=14100/mmc, PMN_s=81%, Ly=15%, Mo=4%, PLT=140000/mmc; ESR = 5/10 mm, Prot. =3,3g/dl; Ca= 6,2 mg/dl; serum colesterole = 53 mg/dl, TG=70mg/dl; serum glucose = 49 mg/dl; Na=116 mEq/l, serum iron=53µg/dl; Adler test positive, stool testing positive, abdominal ultrasound found liquid in peritoneal cavity; Conventional chest radiograph revealed bilateral diffuse interstitial infiltrates perihilar and peribronchial; enlarged cardiac silhouette) the following diagnoses were noted: „Interstitial pneumonia. Malabsorbtion syndrome. Iron deficiency anemia. Cachexy. L. Down disease. Mental delay." The treatment she needed: fluid rebalanced and intravenous aminoacids administration, followed by a high calorie diet; antibiotics: Cefoperazone-Sulbactam. She was discharged respiratory healed, but with the same poor nutritional status, because, in orphanage, she refused food.

Case 3

D.C., 8-years and 8 months (Figure 2), female, with Seckel syndrome, presented as a transport to the Emergency Room Craiova, First Pediatric Clinic, from another county, secondary to altered metal status and cyanosis of the extremities that lasted for about 30 minutes. On physical examination, patient in critical condition, subfebrile, agitated, who had short stature with weight being 13 kg, microcephaly, prominent eyes, the characteristic features of „bird-headed dwarf" (pointed nose, micrognathia), dental dystrophy, sequelae of rickets, spastic cough, dyspnea, tachypnea, bilateral bronchial and crackling rales, the aspiration of oropharyngeal secretions revealed purulent secretions, alimentary vomiting, spastic tetraparesis, mental retardation, her mental age being of an one-year-old child. Peripheral blood examination showed Hb=12.6 g/dl, total WBC= 5300/mm^3, PMN=79%, Ly=11%, Mo=10%, PLT=460000/mm^3. Respiratory tract culture was performed on tracheobronchial lavage and it was positive: Staphylococcus aureus was isolated. Antibiotic susceptibility test result showed the isolated strain was susceptible to Oxacillin, Linezolid, Teicoplamin, Vancomycin, Rifampicin, Ciprofloxacin, Cefoperazone-Sulbactam and resistant to Penicillin. Conventional chest radiograph revealed bilateral diffuse interstitial infiltrates perihilar and peribronchial, with multiple bilateral confluent reticular opacities. The heart size was within normal. According to the result of culture, the patient was treated with Cefoperazone-Sulbactam, symptomatic medications, fluidifiants of bronchial secretions, oxygen therapy, anticonvulsivant therapy. In pediatric intensive care unit as well as in pediatric ward where she was transferred subsequently in stable condition, her evolution was favorable. After three days from admission, she has got no fever anymore. Prior to discharge, the patient had resumed normal activity.



Figuure 2: DC-her mother accepted.

Case 4

P.E.R., 8-years female and 7 months (Figure 3), with a past medical history of spastic tetraparesis and intellectual disability, presented as a transfer to the pediatric intensive care unit from an outlying hospital, secondary to altered mental status, due to seizures associated with fever. The patient was born at term by C-section due to umbilical cord around her neck and needed neonatal intensive care. When she was 2-years-old the treatment Pyritinolum was initiated by a pediatric neurologist. On examination, short stature with weight being of 10 kg, Glasgow coma score 10, lethargy, sleepliness, T= 37.9°C, HR= 170, dry skin and mucous membranes, shrivelled and dry skin that lacks elasticity, upper airway sounds transmitted throughout, good bilateral breath sounds, decreased urine output, nuchal rigidity. Peripheral blood examination: Hb=10,4 g/dl, WBC=12000/mm^3, PMN=47%, Ly=22%, Mo=4%, 300000/mm^3, ESR: 25 mm/hr, Astrup parameters: pH=7.29, pCO_2=33.4, pO_2=38.8, hypernatremia (160.6 mmol/L), hypokalemia (2.93mmol/L), hyperglycemia (256 mg/dL), ALT: 14U/L, AST: 60U/L. Ocular examination showed normal aspect of the optic disk and retinal blood vessels. General treatment was started: fluid rebalanced and intravenous aminoacids administration. Then, the patient was transferred to the pediatric ward in stable condition on hospital second day. It has been initiated treatment with antibiotics: Ceftriaxonum, then Cefoperazone-Sulbactam, Gentamicin, that lasted to discharge. The total blood cell count decreased to 8000/mm^3. On the second day of hospitalization, the patient rested with normal temperature. She presented no more seizures. Prior to discharge, girl patient became alert.

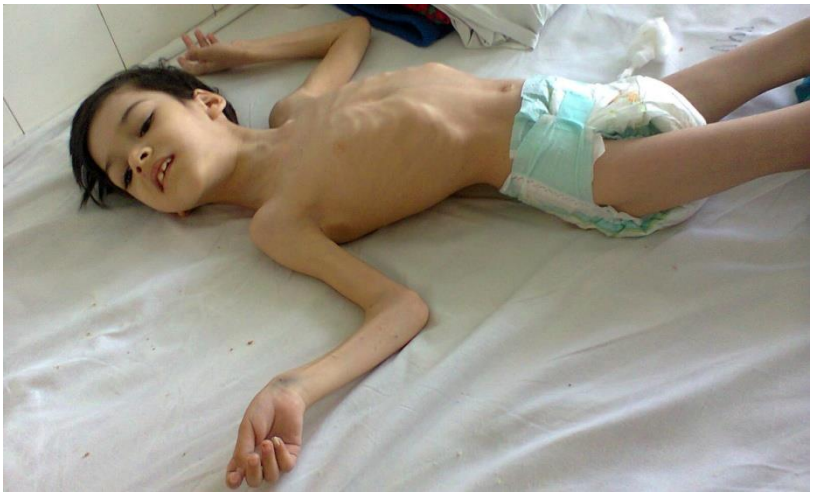


Figure 3: PER-we had mother´s accept.

Discussions

In terms of patient **N.S**. (cachectic, whose BMI= 12, less than 3rd percentile, under 3-rd negative deviation) we note that he fulfilled the diagnostic criteria for sepsis having: fever, leukocytosis, tachycardia. Also, CRP levels greater than 8 times the upper normal and thrombocytopenia can diagnose severe sepsis. In subjects with heart defects, any infection even of the teeth, should be treated with antibiotics, because the risk of bacterial endocarditis is very high. Unfortunately, what we feared for, has happened. Endocarditis with sepsis was vigorously treated with cephalosporins associated with aminoglicosyde, but thrombocytopenia led to fatal intracerebral hemorrhagic stroke. The child, in the context of hypoxia of tetralogy of Fallot, had polycythemia (Hb = 20 g / dl), but even if the initial motor deficit suggested an ischemic stroke caused by a trombus (blood clot), then death was caused by bleeding of cerebral trunk. Obviously, the mother's absence and the heart defect that went uncorrected led to early death. Surgical treatment of congenital heart defects in children with trisomy 21 who live in orphanage, can rarely be performed in Romania. Repeated infections, lack of family love, Fallot disease marked by hypoxia and mental retard (because of institutionalization and genetic disease), shortage of foster care, led to cachexia that favored sepsis and speeded the tragic end. In children with tetralogy of Fallot, cared and loved in family, survivals were recorded even up to 16 years without surgery, but with a good nutritional status.

P.S girl patient with W = 9 Kg and H = 83 cm, compared with normal age, meaned the common measures in four years, W = 17 kg (corresponding to the 50th percentile and SD 0-1) and H = 100 cm (height mean age) found: She wasn't very stunted (83% of the average of her age height) but underweight (extremely low weight for age, 50 percent of normal) and wasting (extremely low weight for height, under 70 percent). She had BMI (PI)= 13, less then 5th percentiles and under 3-rd negative deviation (according to WHO 2007 children growth). Based on laboratory data, we found: hypoglycemia, hypoproteinemia (with edema and peritoneal fluid), hypocholesterolemia, hypocalcemia, iron deficiency anemia, hypotension. The

patient had no bradycardia neither bradypnea, but she lacked Bichat's bubble (like the other three). In conclusion, the patient had a typical third degree malnutrition. VSD (ventricular septal defect) partially explains cachexia, being incriminated other factors, such as: genetic disease, institutionalization, lack of family, lack of appetite due to repeated infections, malabsorption correlated with duodenal stenosis corrected perinatal. It should be remembered that severe malnutrition cause intestinal villous flattening and lactase deficiency, leading to malabsorption, that maintains cachexia. We also know that heart malformations without cyanosis associate often severe distrophy.(14)

Girl-patient **D.C**. 8 years, 4 months, BMI=13, had the particularities of Seckel syndrome (characteristic features of „bird-headed dwarf", microcephaly, pointed nose, micrognathia) and was diagnosed with Staphylococcal pneumonia. Staphylococcal pneumonia can develop a staphylococcal pleurisy and is considered a severe clinical form of pneumonia. In the case described, despite of a genetically-Seckel-syndrome, pneumonia was not complicated, being treated with an antibiotic to which Staphylococcus aureus was susceptible: Cefoperazone-Sulbactam. As all genetic diseases, in the Seckel syndrome there is a greater susceptibility to infection. In this case, it was a community-acquired seed of Staphylococcus Aureus,(receptive to Oxacillin) and the patient was discharged cured. The difference, in her case, was the mother's presence. Patient's vital prognosis can be improved by love and good care.

Patient girl, **P.E.R**., aged 8 years 9 months, with G = 12 kg (BMI= 12), was admitted to the Pediatric Clinic in March 2014 for high fever (40-41◦C), febrile seizures (first episode) refusing food, malaise. Laboratory investigations revealed hyperglycemia (initially 290 mg/dl, then was 170-211mg/dl in ENP with Ringer, 295mg/dl), neutrophilic leukocytosis, thrombocytopenia, elevated ESR. Based on fever, neutrophilic leukocytosis, thrombocytopenia, hyperglycemia, we found severe sepsis as diagnosis. Cachexia associated with hypoglycemia met frequently, especially in the conditions of starvation. In this case, it was necessary differential diagnosis of diabetes onset. Because blood sugar returned to normal without insulin, as the infection heals, the conclusion that was imposed hyperglycemia in context of severe sepsis with unknown origin.

Conclusion

From all admitted patients in last two years in First Pediatric Clinic, Craiova, the incidence of cachectic children was 1,5%. But cachexy was involved in 25% percent of children who died. Only the boy who suffered from endocarditis led him to MODS and death; the three girls were discharged healed. Trisomy 21 caused immunodeficiency and cachexy also permitted severe infections. The etiology of poor nutritional status was combined: congenital defects, improper diet, frequent infections, inadequate care (two patients lived in orphanage, two girls had single mothers). Pneumonia is frequent in thin children, with birth malformations. Congenital heart defects could have been complicated to endocarditis. Cachexy in malformed children is an important cause of immunodeficiency that leads to severe, sometimes letal infections. Infections produce denutrition and cachexy promotes severe sepsis, especially in parentless children.

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CORELATION BETWEEN NEONATAL SEPSIS AND CHOLESTATIC JAUNDICE IN A CASE OF PREMATURE NEWBON

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Abstract

Sepsis is a major cause of morbidity and mortality in newborns, especially in premature babies due to associated immunological deficiencies and comorbidities. Although not common in medical practice, secondary cholestatic jaundice raises major problems, and the three entities - sepsis, cholestatic jaundice, prematurity - may cause or exacerbate the vicious circle of prolonged neonatal jaundice, because of difficulties in diagnosis and treatment . Thus the prognosis is often poor and the evolution of the disease with multiple complications. Case Presentation: This is the case of a premature infant with very low birth weight (VLBW) with associated pathology, who developed cholestatic jaundice. Severe neonatal sepsis and prematurity accounts for pathologies that can cause and aggravate the jaundice with immediate and remote neonatal complications. The determinants of neonatal cholestasis: infectious, obstructive, genetic, metabolic, endocrine. The intricate causes led to the complicated evolution and prolonged hospitalization. Conclusions: Gestational age must be documented for each newborn and it is an important predictor of the risk of developing hyperbilirubinemia. Neonatal sepsis associated with prolonged jaundice will complicate the evolution and TORCH pathology is difficult to be ruled out. Obstructions or anatomical malformations of bile ducts are difficult to detect by imaging methods in this group of patients, very low birth weight being an impediment to the investigation.

Key words: prematurity, sepsis, prolonged cholestatic jaundice

Introduction

Sepsis is the leading cause of neonatal mortality, despite the progress of modern medicine, having been reported annually over 6 million deaths. [1] Early-onset neonatal sepsis is caused by infections acquired through maternal-fetal transmission, and the late-onset nosocomial always. Onset is much faster in premature infants. In prematurs with VLBW, due to the need of prolonged hospitalization periods,the risk of developing late-onset sepsis is higher. [2] Identification of the risk factors and the proper use of protocols for diagnosis of neonatal sepsis with prompt and appropriate treatment, will decrease the hospitalization days and the mortality and morbidity of newborns. [3]

The risk of developing severe jaundice is inversely related to gestational age. Premature infants will have increased risk of developing bilirubin encephalopathy thus they require careful monitoring of total serum bilirubin. Cholestasis, defined as a decrease in the secretion of bile flow due to damage to the hepatocyte or bile flow obstruction with intrahepatic bile ducts extra or is caused by any condition which substances normally excreted in the bile are retained.

Case Presentation

The newborn B. M. female was hospitalized at 4 days of life in ICU of Premature Children Emergency Hospital "Louis Turcanu" in Timisoara. The newborn was born by Caesarean section in cephalic presentation at a gestational age of 32 weeks, with birth weight 1080g and IA = 5 at 1 minute. Please note that in the delivery room required positive pressure ventilation and cardiac massage.

On admission showed a serious general condition, jaundice of the skin and sclera; repeated episodes of apnea, arrhythmia and respiratory distress, with biological samples conclusive for sepsis.

Admission laboratory data confirmed the jaundice: BD = 27.57 umol / l, BT = 162.35 umol / l. She presented with changes in blood count with severe thrombocytopenia (Le = 4.470 UI, Hb = 16.2 g / dL, Ht = 47%, PLT = 1,000 IU). Inflammatory markers were elevated (CRP = 110.56 mg / L, procalcitonin = 77.37 ng / ml) with positive blood cultures for Klebsiella Pneumonia (48h).

Evolution during hospitalization was slow, with a slow upward curve weight (from 1050 to 2560g). It required O2 therapy with VM due to multiple episodes of apnea episodes and psychomotor agitation. Sclero jaundice - skin persisted throughout the period of hospitalization, with mild but never full remission episodes. In evolution the newborn developed bilious vomiting , distended abdomen, acholic stools, meteorism. Dark urine emerged late in evolution, from 76 days of life with favorable outcome.

Inflammatory samples became negative but increased CRP persisted during hospitalization under poly-broad spectrum antibiotics. (Fig. 1)

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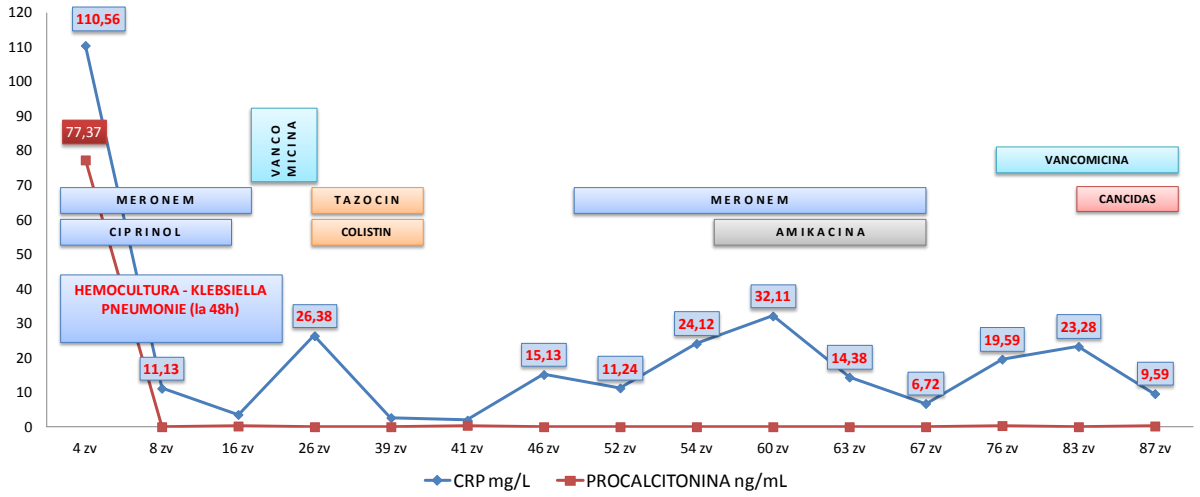

Fig. 1. Evolution of inflammatory markers, dynamics.

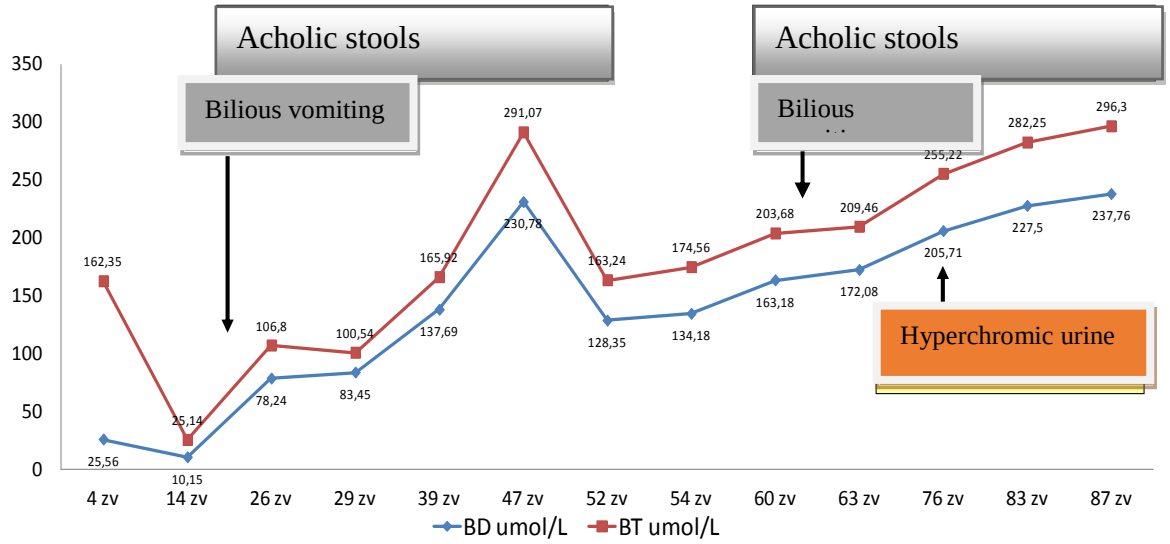

Fig. 2. Hipebilirubinemia, dynamics.

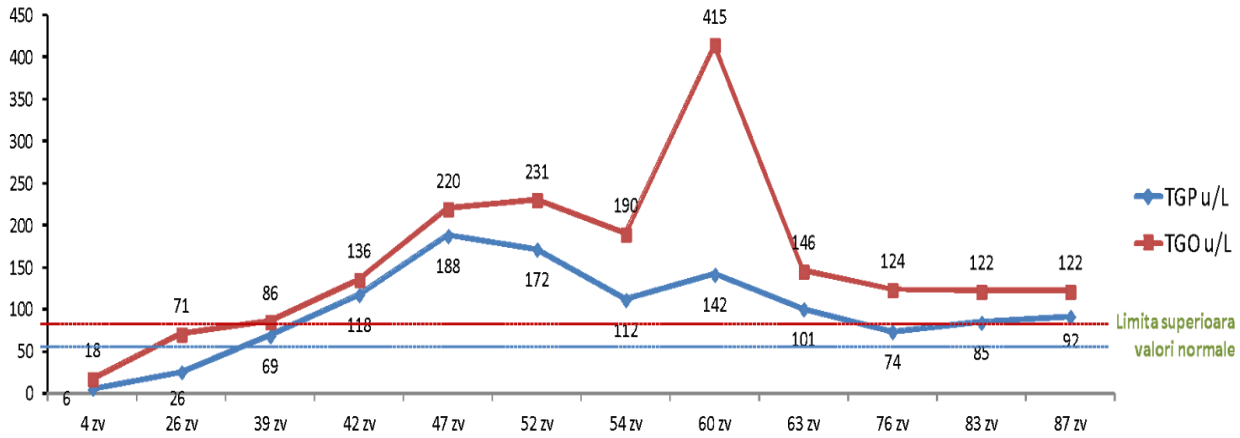

Fig. 3. Evolution of transaminases, dynamics.

Table 1. Causes of neonatal jaundice.

NEONATAL CHOLESTASIS		
Infectious		**Genetic (25%) , metabolic (20%), endocrine**
Viral	adenovirus; cytomegalovirus; coxsackievirus; Epstein-Barr; echovirus; enterovirus; hepatitis A, B, or C; herpes simplex; human immunodeficiency virus; parvovirus; rubella	Prematurity
Bacterial	urinary tract infection, sepsis, listeriosis, tuberculosis	A1AT deficiency (10%)
Parasites	toxoplasmosis, malaria, toxocariasis	Bile acid synthetic defects
Spirochete	syphilis, leptospirosis	Alagille syndrome, Crigler-Najar syndrome, Gilbert syndrome
Histoplasmosis		Hypopituitarism (septo-optic dysplasia) Hypothyroidism
Anatomic obstruction		Hereditary spherocytosis Elliptocytosis G6PD deficiency Thalassemia Vitamin K induced hemolysis
Biliary atresia (23-35%) Choledochal cyst or other congenital bile duct anomaly		Autoimmune hemolytic disease Polycythaemia Galactosemia
Congenital hepatic fibrosis Inspissated bile syndrome		ABO incompatibility Rh isoimmunization
Neonatal sclerosing cholangitis		Cystic fibrosis
Tumor/mass		Drugs / hormones (progesterone)
Increased enterohepatic circulation of bilirubin		**Other**
Pyloric stenosis Intestinal atresia Ileus		Ischemia-reperfusion injury Perinatal asphyxia Hemophagocytic lymphohistiocytosis Idiopathic neonatal hepatitis Neonatal lupus erythematosus

Adapted from [4]

Determination of total and direct bilirubin in dynamic shapes, prolonged jaundice biological picture (Fig. 2).

Initially, transaminases were within normal limits, will exceed the upper limit of normal at 42 days of life and keep it elevated throughout the hospitalization (Fig. 3).

Other biological investigations Task:

− examination stool digestion starch - absent, muscle fibers - absent, fat - absent

− ELFO: albumin = 70.4% = 2.7% α1, α2 = 9.7%, β = 10%, δ = 7.2%

− Thyroid hormones (41 zv): FT3 = 2.63 pmol / L FT4 = 14.92 pmol / L, TSH = 1.56 IU / L

− cytological examination blood smear: anisocytosis, moderate anizocromy isolated red blood cells in the target Pile (50 days old) , anisocytosis, hypochromia (69 days old)

− osmotic resistance: Initial <4.2 ‰, total <2.8 ‰

− tests hemolysis: Percentage = 3.6% hemolysis, hemolysis percentage corrected glucose = 2.3%

− Test Brever - Negative

− Toxo IgG (IU / ml): Negative

− CMV IgG (U / ml): Positive (on 2 consecutive measurements)

Imaging investigations performed for prolonged jaundice etiology and complications of prematurity with VLBW for detection:

− Echocardiogram: septal defect 3-4 mm perimembranos with both shunt shunt VS-VD and VS-AD type Gerbode, VS-AD Vmax = 4.3 m / s, P max = 77 mmHg and VS-VD Vmax = 2.3 m / and P max = 23 mmHg, foramen ovale

− ETF: intraventricular haemorrhage gr II / III. Periventricular leukomalacia average form

− Eye exam: OD / under vascularized retina, OS / ROP stage 1 in zone II. At a second consultation over 18 days ROP in remission, with favorable evolution.

− Abdominal ultrasound (34 zv): Liver - normal aspect, with the longitude = 49 mm. Normal ESR. Gallbladder - hypoechogenic content with transonic zone with a large expansion of bile duct (bile duct cyst). RS - 35/15 mm, RD - 33/25 mm, echostructure normal. Stomach distended with food content. Spleen slightly oblate - 33/25 mm. Thick bile syndrome is suspected.

− MRCP (57 zv): Liver, pancreas, spleen, kidneys, adrenal normal aspect native investigation. Gallbladder plied, relaxed. Extrahepatic biliary duct normal. Without ascites. Without lymph intra / retroperitoneal. VCI, abdominal aorta normal size.

Discussion

VLBW preterm infant developed neonatal sepsis and required parenteral nutrition.

After imaging investigations a cyst of the bile duct cyst was found. All these factors have caused and prolonged the neonatal jaundice.

Multiple causes of cholestatic jaundice in the literature are cited.

Neonatal cholestasis is characterized by an increased serum level of BD in the first 90 days. Cholestasis indicators are: BD serum levels> 17 micromol / L or 1 mg / dl, or BD serum level of> 20% of BT concentration (if BT is> 85 micromol / l or 5 mg / dl) [10] [11].

Neonatal cholestasis affects about 0.04 to 0.2% of newborns. According to the literature about 40-60% of cases of cholestasis are associated with prolonged parenteral nutrition, the rest of the etiologies cases occur due to the following:

Energy demand is of great importance. The growth deficit is secondary to failure of fat absorption, impaired metabolism of proteins and carbohydrates, as well as increased metabolic demands. Oral nutrition is the preferred route of administration. In most cases additional vitamins (K, E, D) are required. [8], [9]

Short-term prognosis is unfavorable, with evolving jaundice and low survival rate due to multiple comorbidities (neonatal sepsis, anemia mixed prematurity, infection). In the long term, according to some authors (Robertson and Howarth), permanent deafness may occur (3.1% of cases) or severe hearing loss (1.9% of cases) if VLBW preterm [5]. Extension brain damage and retinopathy of prematurity may predict risk of severe disability at age 11 major. [6] proinflammatory molecules due to sepsis may have a negative effect on neurological development with cognitive impairment and cerebral palsy. [7]

Prognosis is worsened by hepatic impairment due to the evolution of liver cell destruction , low weight due to prematurity and disease, intraventricular hemorrhage and periventricular leukomalacia evolving toward psychomotor retardation.

Conclusions

VLBW preterm represent an impediment to the necessary investigations to establish the etiology, low birth weight is a morbid entity (the major factor increasing bilirubin).

Gestational age is a major predictor of risk of developing hyperbilirubinemia (jaundice extended) and should be evaluated and documented for each newborn.

The combination of multiple factors: early neonatal sepsis, prematurity, prolonged partial parenteral nutrition had a major role in the persistence of cholestatic jaundice.

Imaging studies are useful to detect gallstones or biliary malformations intra or extrahepatic. This may use ultrasound and endoscopic retrograde cholangiography MRCP with contrast material.

Velasco Cerrudo (16) tries in 1992 a score of practical use.

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INFLUENCE OF PREGNANCY EXTRINSEC FACTORS ON INTRAUTERINE GROWTH RETARDATION AND ANEMIA IN NEONATES IN TIMIS COUNTY - ROMANIA

Georgeta Noditi[1], Gluhovschi A[2], Diana Anastasiu[2], Cristina Dragomir [1], Ileana Enatescu[3]

Abstract

Introduction. The aim of this study was to correlate the mother's biological status and related extrinsic factors during pregnancy and growth retardation and anemia in neonates. Material and method. We have done a prospective study on 75 mothers who delivered in 2013 in Obstetrics and Gynecology Clinics of Emergency County Hospital Timisoara and their newborns. Maternal extrinsec factors pre- or during pregnancy were related with the percentage distribution of neonates with IUGR and anemia. Results. Smoking habits (53%), lack of education (44%) and precarious socioeconomic conditions (42.7%) were the first three extrinsec factors well represented. The percentage distribution of newborns was 43% AGA, 32% with IUGR and 25% with IUGR and anemia. The overall percentage of newborns with IUGR is 57%. Conclusions. Extrinsec factors present pre- and during pregnancy influence the increase of neonates with IUGR inself or IUGR and anemia.

Key words: IUGR, anemia, maternal extrinsec factors.

Introduction

Preconception health can potentially improve women's health and pregnancy outcomes (1). Fetal growth and development is a complex process that depends on the biological status of the mother as well as on many factors including socio-economic conditions, education, risky behaviors, nutrition, ethnic customs, emotional and pathologic burdens and others.

Intrauterine growth retardation (IUGR) describing a fetus that has not reached its genetic growth potential (2) remains one of the main challenges in maternity care (3). Ussually IUGR is accompagned not only with stillbirth, neonatal death, and perinatal morbidity but also with delayed effects like cerebral palsy and diseases in the adult life (4, 5, 6). Many factors related to the mother could have a detrimental impact on fetal growth. For instance, maternal smoking and gestational hypertension are important risk factors for the development of IUGR (2).

The aim of this study was to assess the influence of maternal related extrinsic factors on growth retardation and anemia in infants.

Materials and methods

In 2013 we have studied prospectively the medical records of 75 mothers and their newborns from the Clinics of Obstetrics and Gynecology of Emergency County Hospital Timisoara. We have evaluated the percentage distribution of extrinsic factors available from maternal data: age, ethnicity, socio-economic status, education level, toxic working place environment, nutrition (intake of supplements during pregnancy), obstetrical history, alcohol and tobacco consumption. After registering the infants with IUGR and anemia we have compared the distribution of neonates with appropriate gestational age (AGA), IUGR and IUGR+anemia.

Results

In 2013, 75 mothers who delivered in the Clinics of Obstetrics and Gynecology from Emergency County Hospital Timisoara and their newborns were studied prospectively. The mean age of the mothers was 30.2 years.

In table no 1. we have analyzed the maternal extrinsec factors present pre- and during pregnancy. 33.3% of mothers are belonging to an ethnic group that is actually quite consistent in our country and for whom medical surveillance is not necessary, due to religious and other beliefs. 42.7% of mothers are living in precarious conditions with low and some with no monthly income. Another characteristic was lack of education for 44%. Unfavorable working place was encountering in 7% of mothers. Only 7% of mothers have used nutrition supplements (under medical prescription) during pregnancy.

Out of 75 mothers, less then half (44%) had at least one medical check during pregnancy and 15 out of them were aware of having anemia pre- and during pregnancy.

More than half of the mothers (53%) have been smoked during pregnancy. None of them admitted alcohol consumption during pregnancy.

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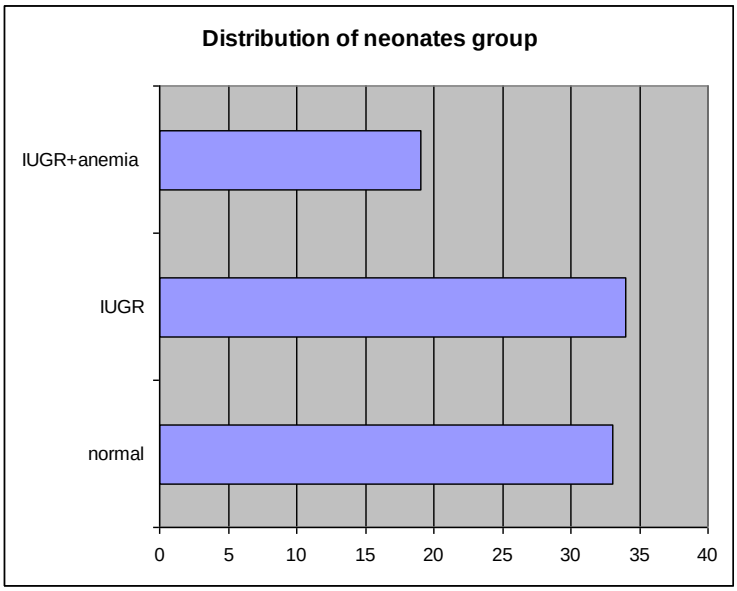
Table 1. Maternal extrinsec factors pre- and during pregnancy.

Ethnic group	Precarious socioeconomic status	No Education	Toxic work place	Nutrition supplements	Obstetrical history	Smoking habits
33.3%	42.7%	44%	7%	7%	20%	53%



Graphic 1. Distribution of neonates with AGA, IUGR and IUGR+anemia.

Discussions

Fetal growth and development depends on maternal preconception and during pregnancy health. For instance, anemia may affect up to 56% of pregnant women in developing countries (7). In our study 20% of mothers were aware of being affected by anemia before and during pregnancy. All of them were diagnosed in the first trimester and no correction was succeeded in the next two trimesters. Iron deficiency during pregnancy can have severe consequences, not only for the mother, but also for her infant. Maternal iron deficiency has been implicated as a risk factor for preterm delivery, small-for-gestational-age and neonatal mortality (8).

Maternal smoking is an important risk factor for the development of IUGR (2, 9). In our study smoking habit was recorded in more than half (53%) of mothers. Another characteristic was that 42.7% of mothers were living in precarious conditions with low or some with no monthly income. Lack of education has been encountered in 44% of mothers.

Growth failure is often not detected antenatally, and in routine clinical practice, as many as three-quarters of babies at risk of IUGR are not recognized as such before delivery (10). Different aethiologic factors are recognized as conditions for onset of IUGR, i.e., placental insufficiency, congenital anomalies, infections, or drug and substance misuse (3). Mortality and morbidity are increased in IUGR infants compared with infants who are appropriate for gestational age (11, 12). Considering our study, we observed a percentage distribution of newborns: 43% appropiate gestational age (AGA), 32% with IUGR and 25% with IUGR and anemia.

Maternal behaviors and chronic conditions such as tobacco use, inadequate folic acid intake, are prone to IUGR and anemia in neonates (1). Improving educational opportunities, health-related behavior and access to health care (13) could reduce the risks and not ultimately different inequalities in health in the EU countries for instance (13).

Conclusions

Analyzing the data from this study we consider that many maternal extrinsec factors are detrimental on normal fetal growth and anemia in neonates.

Women's prepregnancy and interpregnancy health status, pregnancy and infant outcomes should be under constant care of medical services and thus access to health-care could be improved.

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PROPRANOLOL TREATMENT IN INFANTILE HEMANGIOMA

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Abstract

Infantile hemangiomas are the most common benign tumors of childhood and their management could be chalanging, especially in those situated in areas with cosmetic impact or possible complicated with functional impairment. We present five cases treated in our department with oral propranolol, with good and excellent results.

Key Words: hemangioma, propranolol, vascular tumors, treatment.

Introduction

Infantile hemangiomas are the most common benign tumors of childhood, with a very large spectrum of disease which make difficult to define a standardized approach to the management, mainly because of the unpredictability of the natural course: involuting or non-involuting. (Tan et al, 2011)

The incidence of these soft tissue tumors is about 5%, higher in girls and premature infants; usually, these tumors appear in the neonatal period, progressively grow in the first year of life and then stop growing or involute during the next years. (Bruckner et al, 2003) The spontaneous regression is unpredictable in terms of the final aspect of the lesion, sometimes the involution being very modest, with marks and scars in the end. Sometimes, complications such ulceration, infection, bleeding, markedly growth, pain, functional impairment, can occur. (Enjolras et al, 1997) The psychological aspects of the cosmetic problem, even in simple cases and more important in cases with anatomical distorsion, should also be considered. (Mulliken et al, 1982; Tanner et al, 1998)

The therapeutic arsenal includes systemic corticosteroids, vincristine, cyclophosphamide or local injection with interferon alpha 2 a, bleomycin, alcohol, corticoids, specialized dressings, pulsed-dye laser, cryosurgery, surgical excision. (Talaat et al, 2012) In 2008, Léauté-Labrèze observed the rapid involution of a large facial hemangioma when propranolol was used for the treatment of a steroid induced hypertrophic cardiomyopathy. (Léauté-Labrèze et al, 2008)

Propranolol is a selective β-adrenergic antagonist which competitively inhibits β1 and β2 receptors and due to its lipophilic properties has also membrane-stabilizing properties. The exact mechanism of action is still unknown, but it was hypothesed that it interferes with vascular tone, angiogenesis, apoptosis of vascular endothelial cells. (Storch et al, 2010)

Patients and methods

We present a photo gallery of five cases with proliferative infantile hemangioma treated in the Emergency Children Hospital Iasi, Romania in the last two years. Before initiation of propranolol treatment, the regimens and potential risks were clearly explained to the parents and their informed consent for therapy and use of the photographs was obtained; a full medical history of the child was taken and then vital signs, physical examination, specific investigation were performed in order to rule out any contraindication for the treatment. The patients were initially treated with 1 mg/kg/day divided in two or three doses, the first dose being taken in the hospital and the baby monitorized for glycemia, cardiac frequency and blood pressure. The first follow-up visit was scheduled after one month, when the dosage was adjusted with the weight and according to the clinically response. The next visits were scheduled at a three months interval the treatment being continued until the lesion completed involuted or the baby reached one year of age, or, for the older babies, when no regression seems to be evident between two visits.

Results

The results were good, with acceptable cosmetic of the lesion in the cases where the resolution was not complete. No complications were noticed during the follow-up.

Case 1: A 10 months old baby boy, first presentation for a periocular hemangioma (the pictures in the upper line). Propranolol treatment was initiated; the follow-up shows resolution of the hemangioma: 1 month (left, lower line) and four months (right, lower line) after the treatment was started (Fig. 1).

Case 2: An 3 months baby boy with an superior eyelid hemangioma, with visual axis impairment at the presentation (picture in the left upper line); from left to right, up to down pictures at one, two and six months after the treatment was initiated, with complete resolution of the tumor(Fig. 2).

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Case 3: A three months baby boy, prematurely born, with a tuberous hemangioma of the zygomatic area; on the left one month after the treatment was started, in the lower line left picture at three months after and right picture at one year (Fig.3).

Case 4: A three months girl with a lip hemangioma (upper line, left picture); follow-up at one, three and five months later, with almost complete resolution of the tumor (Fig.4).

Case 5: An eight months old girl with ulcerated hemangioma of the labia and follow-up at one, three and six months after the treatment was started (Fig. 5).

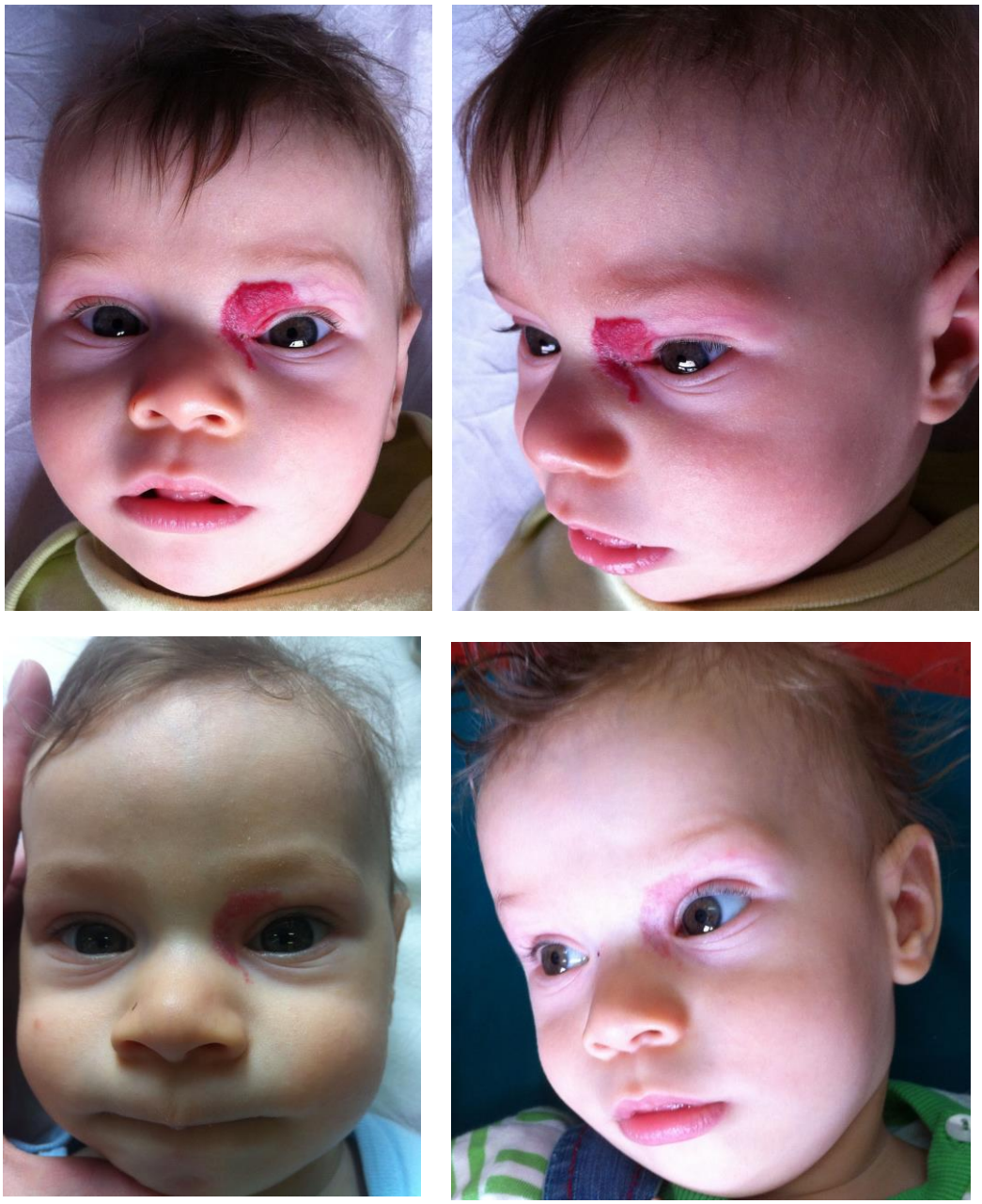

Fig. 1. Case 1 periocular hemangioma.

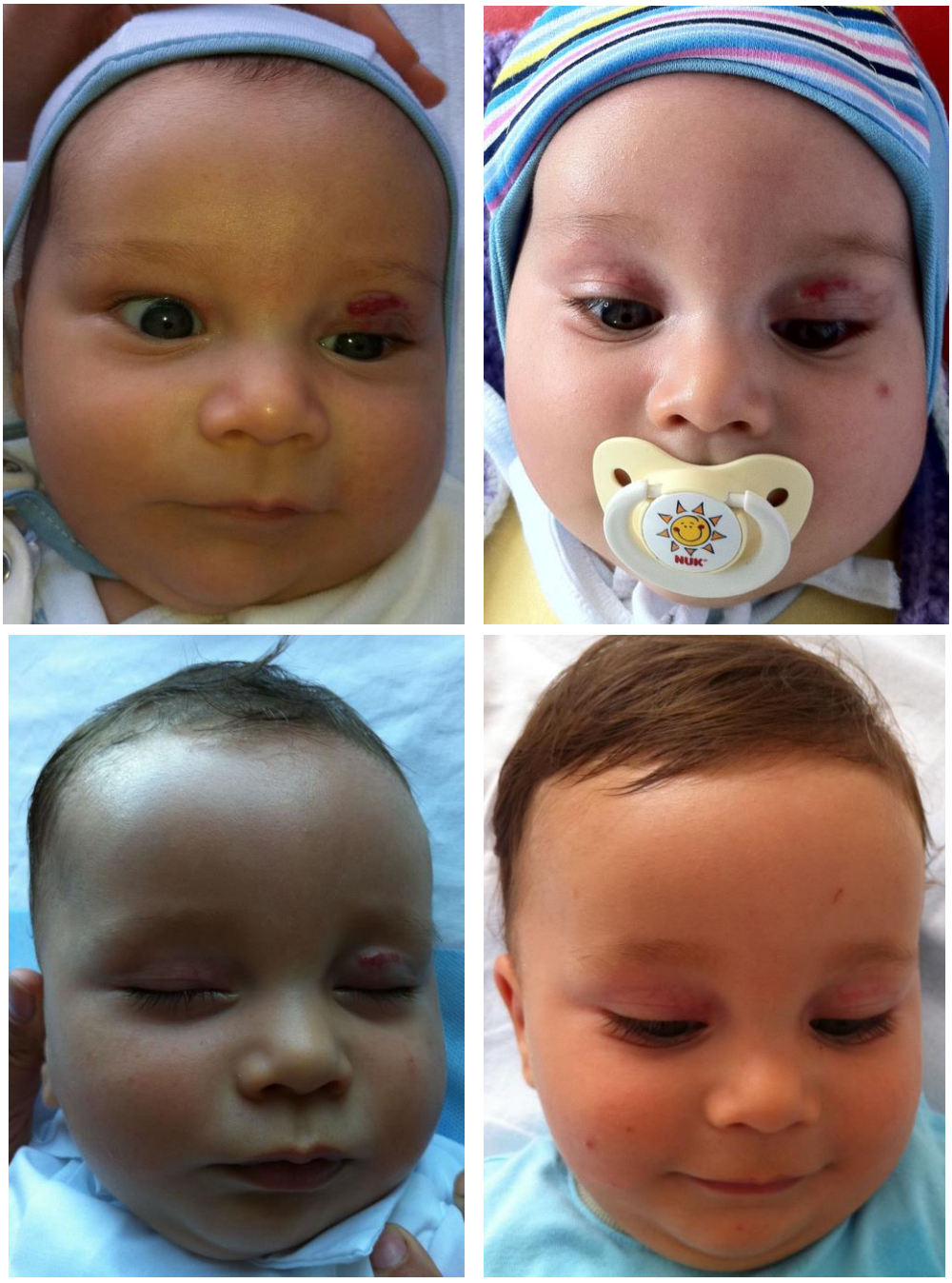

Fig. 2. Case 2 superior eyelid hemangioma.

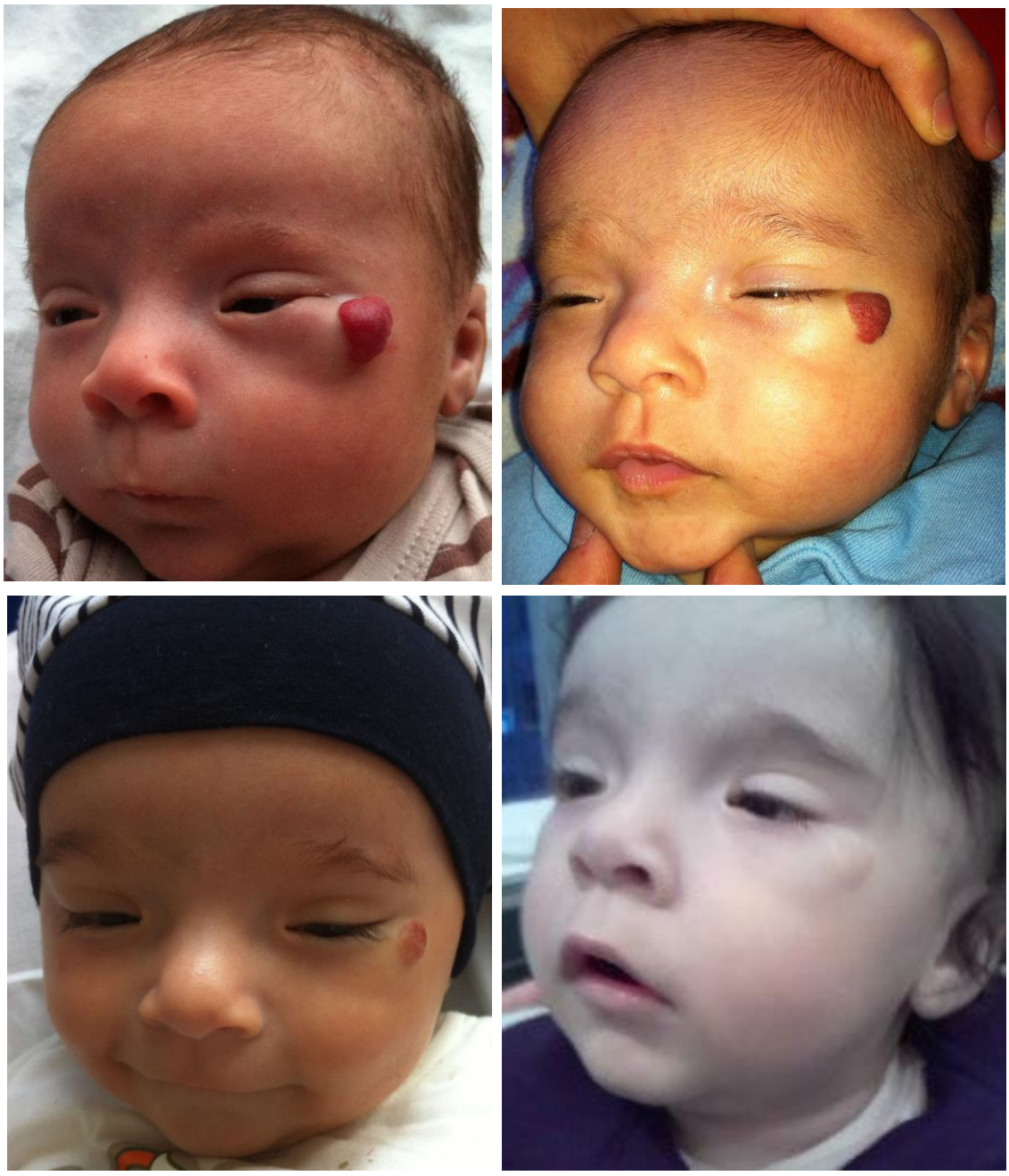

Fig. 3. Case 3 a tuberous hemangioma of the zygomatic area.

Fig. 4. Case 4 lip hemangioma.

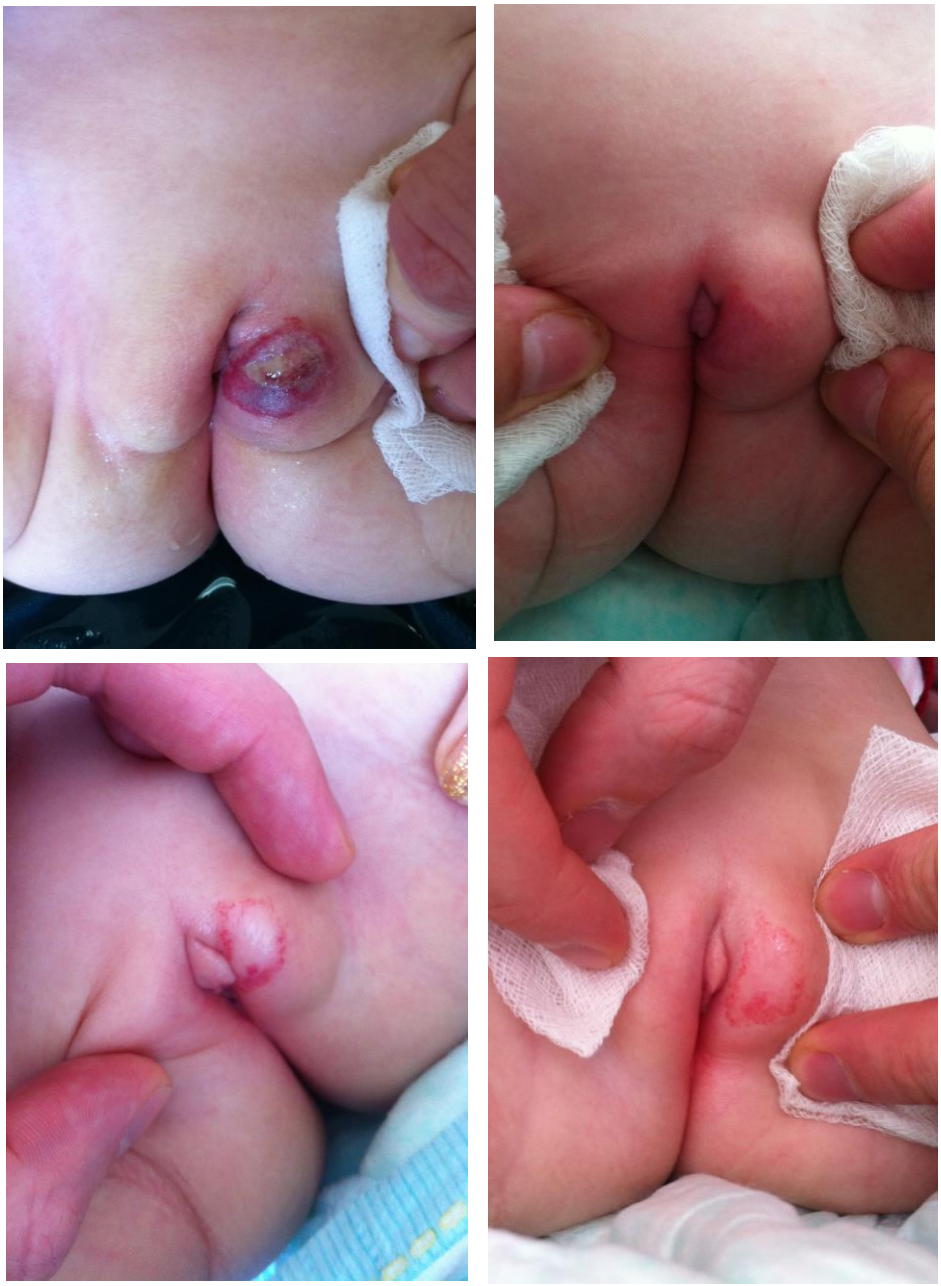

Fig. 5. Case 5 ulcerated hemangioma of the labia.

Conclusions

Propranolol has shown excellent results in infantile hemangioma and will probably become the treatment of choice for these tumors in the future, especially in those with localizations and complications like above. Potential side effects include bronchospasm, bradycardia, hypotension, hypersomnolence, hypoglycemia, but all these could be avoided by correct monitorizing at the initiation of the treatment and parental education in order to recognize the adverse effects. Further trials are needed to determine the right dose, administration frequency and the protocol of monitoring.

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PROGNOSTIC FACTORS IN THE EARLY POSTOPERATIVE OUTCOME OF ESOPHAGEAL ATRESIA. THE EXPERIENCE OF A TERTIARY CENTER OVER A 5 YEARS PERIOD

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Abstract

Purpose: The aim of this study was to determine the influence of prognostic factors on the postoperative outcome of esophageal atresia patients, taking into consideration loco-regional particular features.

Methods: A retrospective analysis of the medical records of 28 patients diagnosed with esophageal atresia was conducted, using a logistic regression model. Patients had been admitted in our hospital between 2009 - 2014. The survival rate was recorded separately from the independent factors, such as demographic features, weight at birth, the timing of surgical treatment, co-morbidities, postoperative prognosis and management of complications.

Results: According to the Spitz prognostic classification, there were 21 patients in group I (birth weight over 1500 g with no major anomaly), 3 patients in group II (birth weight less than 1500 g or major cardiac anomaly) and 4 patients in group III (birth weight less than 1500 g plus major cardiac anomaly). The mortality rate was 33% in group I, 100% in group II and 100% in group III. The mean birth weight was 2282 g ±2SD, and the mean gestational age was 31 weeks. The age at initial presentation was over 24 hours in 15 patients, with fatal outcome in 13 of them. The cardiac malformations presented as the associated anomalies with the highest risk. Surgical treatment was as follows: primary anastomosis in 21 cases, cervicostomy and gastrostomy in 6 cases, and Foker technique in 1 case.

Conclusions: The analysis of this series indicated a low survival rate for this pathology in our center. Besides the prognostic factors cited in literature (low birth weight and age at birth, associated cardiac malformations), we include, as risk factors for the increased mortality, the delayed diagnosis and presentation at our tertiary center. The further refinement of a multidisciplinary approach towards this pathology would contribute to a higher survival rate and an improved result of the therapeutic management.

Key words: Esophageal atresia, survival rate, gap-length, anastomotic leak, demographic factors

Background

Esophageal atresia and/or tracheo-esophageal fistula represent a congenital malformation with and incidence of 1 per 2500 births, being incompatible with life in the absence of surgical treatment. Improvements in neonatal intensive care, surgical techniques and the management of associated anomalies have determined an increase of survival rate of up to 90% in certain centers[1]. The various proposed prognostic classification systems reflect this favorable outcome. In this study, we conducted a retrospective analysis of survival rates of patients treated in our tertiary center in Romania, using the data and prognostic factors cited in literature, keeping in mind the regional particularities.

Methods and Materials

Twenty eight patients included in our study were treated for esophageal atresia from 2009 to 2014. Respiratory, gastrointestinal and ano-rectal associated anomalies we treated surgically in the same center. Reviewing the medical documents, we gathered information regarding demographic data, birth weight, and anatomical classification of the esophageal malformation, age at surgical intervention, associated anomalies, surgical technique, outcome and management of complications, with the aim of identifying prognostic factors of successful surgical treatment.

Using univariate logistic regression analysis, the relationships between survival rates of targeted risk groups and the demographic parameters, physio-pathological aspects and postoperative complications were studied. Data processing was achieved using IBM SPSS Statistic 20 program.

Results:

There were 19 boys and 9 girls, with a mean gestational age of 31 weeks and a mean birth weight of 2282 g ± 2SD. Fifteen newborns were aged over 24 hours at the initial presentation in the service, of which 11 died from sepsis and pulmonary aspiration lesions. One child was 6 days old at the time of presentation.

Over half of the children which had an anastomotic leak, were diagnosed and operated over 24 hours from birth. Two patients were not born in a medical care unit. Using the Spitz classification system, mortality in group I with 21 patients was of 33% and 100% in groups II and III with 3, and, respectively, 4 newborns.

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For the anatomical ranking of the malformation the Ladd classification[1] was used: 27 type III Ladd cases (esophageal atresia with distal fistula) and 1 case type IV Ladd (esophageal atresia with proximal and distal fistula). The last patient had been initially classified as a type III Ladd, but during a second surgical procedure for an anastomotic leak, the proximal fistula was identified and the classification was corrected. The distance between the esophageal segments and the tension at the site of the anastomosis had been evaluated using preoperative imaging investigations and by clinical observation during surgery. Six patients in the series had the gap between the esophageal ends larger than 3 cm, thus ranging in the "long gap" category.

The cardiac malformations were the most frequent associeted, including 15 minor, non-cyanotic ones and 1 case with an anomaly at the point of emergence of the aortic artery, with fatal outcome within the first 24 hours. Ano-rectal malformations were associated in 4 cases and duodenal atresia in 2 cases. The initial treatment of ano-rectal anomalies consisted in performing a colostomy, simultaneously with the surgical correction of esophageal atresia in 3 cases and after 2 days, in the 4th patient. Duodenal atresia was corrected concomitantly with the esophageal atresia, through a duodeno-duodenal anastomosis.

The period since the time of birth to the presentation in the tertiary center differed, based on the place of birth and proximity to the hospital. The surgical treatment was conducted in the first 24 hours, once the diagnosis was confirmed. Preoperative management included intravenous rebalancing, cardio-respiratory stabilization and aspiring of secretions from the proximal end. Patient evaluation included physical examination, as well as imaging (abdominal x-ray and abdominal, cardiac and transfontanellar ultrasonography).

Surgery was performed in 27 patients, the remaining newborn dying in the preoperative period from complications due to the severe cardiac anomaly. Surgical treatment included: primary anastomosis in 21 cases (through extra-pleural and right posterior lateral thoracotomy), cervicostomy and gastrostomy in 5 cases and Foker technique in 1 case (traction suture on the ends of the esophagus to reduce the distance and delayed anastomosis). A thoracic drainage system was placed in all patients, even though the approach was extra-pleural.

After the primary anastomosis, leakage was present in 6 cases, on an average of 7 days postoperatively. Four of these patients succumbed. In the patients in which cervicostomy and gastrostomy were the first intention procedures, 1 survival out of 5 was recorded. The patient treated with Foker technique presented with anastomotic leakage on the upper esophageal segment, requiring a cervicostomy, but had a fatal outcome.

Due to the hemorrhagic disease of the newborn, sepsis and multiple malformations, death occurred in 16 cases. Most patients had suffered fetal distress at birth. In 6 of the cases with death after the initial surgery, the anastomosis was found intact at post-mortem evaluation. One patient treated with primary anastomosis developed a necrotizing enterocolitis 15 days postoperatively and required an ileostomy and a naso-gastric feeding tube. Thirteen days after this second surgery, the newborn had developed a gastric perforation. The outcome of trying to repair the defect was fatal All complications occurring within one month from initial surgery were considered as Immediate postoperative ones. They consisted in anastomotic leaks, recurrence of fistula, gastric perforation, and suture detachment on the esophageal ends[9].

The initial management of anastomotic leakage involved placing a thoracic drainage tube, antibiotic therapy and feeding through a naso-gastric tube. If these control measures failed, an iterative thoracotomy was made to suture the leaking defect or to perform a cervicostomy and gastrostomy (in 4 cases). Postoperative results were evaluated using plain thoracic x-ray films and eso-gastro-duodenal radiographs with contrast media.

Discussions

The survival rate is the lead parameter through which the quality of management in patients with esophageal atresia is measured. Throughout time, numerous classifications of prognostic factors were described [123]. In 1962, Waterson and colleagues offered the first prognostic classification. Based on a retrospective study on 337 patients treated between 1980 and 1992 in the Hospital for Sick Children on Great Ormond Street in London, Spitz and colleagues showed that low birth weight and severe cardiac anomalies are influential factors in survival rates, if the neonatal intensive care and surgical techniques improve. Okamoto and colleagues have recently revised the Spitz classification system and devised a new one in which they state that in the context of an effective neonatal care of children with low and very low birth weight, severe cardiac anomalies should remain the sole prognostic factor of infants with esophageal atresia. Factors that independently influence the survival rate are, according to Poenaru *et al* [21], severe pulmonary anomalies which require preoperative mechanical ventilation. For the present analysis, the model of prognostic evaluation described by Spitz *et al* was used.

The data described in the literature recommend the initiation of surgical treatment after the first 24 hours, time period during which the cardio-vascular stabilization is obtained, excluding the respiratory distress syndrome that doesn't accelerate the timing of surgical intervention for fistula repair[1, 5]. In the authors' center, all the admitted patients received an emergency surgical treatment, even though their respiratory condition hadn't required an emergency procedure.

Reviewing the Spitz classification, the survival rate in our study is lower than the one cited in literature, 60% versus 93% in group I, with a 100% mortality rate in the rest of the groups. As parameters used to evaluate the outcome, besides low birth weight and age, we have included, as particular features: the time between the moment of birth and the initial presentation in the authors center and the delay in diagnosis. These parameters can lead to a higher risk of complications, such as aspiration pneumonia,

hypoxic brain damage, infection with pathogenic bacteria and altered functional status.

No patient in the present study had been diagnosed antenatally. The prenatal diagnostic rates of this condition are between 30 and 50%. Although the antenatal diagnosis doesn't improve the outcome, it offers a few advantages: the need of further evaluation for detecting associated malformations that can necessitate immediate surgical treatment (keeping in mind that esophageal atresia is not a surgical emergency), reduced time until initial presentation or birth programming close to a pediatric surgical unit and parental counseling to reduce the postpartum maternal anxiety. Lack of these logistic advantages represents a reflection of the insufficiency of territorial healthcare standards and of the quality of antenatal and neonatal care, that influence the morbidity and mortality of these children.

There are numerous case series in the literature that have described the evolution of patients with esophageal atresia through documenting the rate of complications, but few of the authors have tried identifying a direct relationship between the preoperative factors and the complications. The connection between the tension at the site of anastomosis and the anastomotic leak in the postoperative period was described by Kosloske et al[19]. In the authors' center, this distance was measured radiologically (by counting the number of vertebrae between the esophageal ends), and intraoperatively, through direct examination[8]. Anastomotic leak stands as the fiercest complication, as it can lead to a life-threatening pneumothorax. There are current debates regarding the choice of conservative versus surgical approach in anastomotic leak scenario, with a tendency for the first option in most centers, by placing a thoracic drain, together with antibiotic and supportive treatment (parenteral nutrition and ventilation), until remission. There are no sufficient published data analyzing the long term outcome of these patients, including the risk of stricture development due to scar tissue, fibrosis around the anastomosis site, gastro-esophageal reflux, tracheomalacia and worsening of esophageal motility[17].

In the study series, we recorded 6 anastomotic leaks, treated conservatively at first, but which ultimately required iterative thoracotomy, to suture the defect. In 5 of these cases, the evolution was unfavorable, imposing the performing of cervicostomy and gastrostomy. Postoperative incidence of anastomotic leak was 29%, higher than in published studies (around 15-20%) [7,8,15].

For various logistic reasons and taking into account the center's inexperience in minimal invasive approaches during the study period, thoracotomy was the preferred surgical approach. Literature statistics show that results after thoracoscopic approaches are still debatable, due to the high rates of complications and the existence of a steady learn curve[3].

Associated cardiac anomalies may cause problems in alimentation, with newborn fatigue during feeding; therefore a differential diagnosis needs to be made to discover the etiology of apnea (cardiac or respiratory). Except for 1 patient, no other children included in this study had life threatening major cardiac anomalies.

Ano-rectal anomalies as well as those of the gastro-esophageal tract (hypertrophic pyloric stenosis, duodenal atresia) may influence the postoperative evolution, as it happened in 6 of the patients in this study, death occurring rapidly in those with triple association (esophageal atresia, ano-rectal malformation and duodenal atresia).

Though birth weight and gestational age, the type of birth, the time until diagnosis, the immediate postnatal care are all unspecific factors, they may contribute to the status of these patients and should be considered prognostic factors in establishing mortality rates and the immediate development of complications.

Conclusions

The evaluation of this series clearly shows the occurrence of an upgrade of intensive neonatal care, anesthesia and performance of the surgical techniques in the authors' center. Nevertheless, the survival rates are still low. The results show that, due to the diagnostic delay and the late initial presentation in our center, the rise of mortality is obvious. The absence of an antenatal diagnostic suspicion, the poor pregnancy monitoring and the late presentation at medical centers may all lead to delivery occurring at hundreds of kilometers away from a tertiary center. The improvement of medical education of pregnant women, a correct management of the newly born which include the early detection of esophageal atresia, should be obtained through a multidisciplinary approach of this pathology, involving general practitioners, gynecologists, neonatologists and pediatric surgeons.

Complications prevention, improvement of survival rates and of long term outcomes, would require further investigations on implementing better surgical techniques, involving special instrumentation and materials (sutures, transanastomotic feeding tubes, drainage tubes). The evaluation of known prognostic factors in a prospective manner, keeping in mind the regional features, will allow a future decrease of postoperative morbidity and mortality in neonates with esophageal atresia.

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UPGRADE OF THE PERINATAL PROTOCOLS THE IMPACT ON VERY LOW BIRTH PREMATURE BABIES OUTCOME

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Abstract

Introduction: The study has been conducted in the "Filantropia" OG Clinical Hospital, before and after the review of obstetrical protocols for high premature birth risk pregnancies, as well as the protocols for respiratory distress syndrome in premature babies, specific for the neonatology department.

Aim: The impact on morbidity and mortality in very low birth weight (VLBW) premature babies.

Methods: This is a retrospective study comparing premature babies with VG<34 weeks, born between 2012 (n=96) and 2013 (n=150) in Filantropia Maternity. Starting with 2013, the following protocols were updated: perinatal care of pregnancies at risk for preterm birth, resuscitation and stabilizing the premature babies within the delivery room, supportive treatment and standard care of premature babies with SDR. The motivation behind this study was to verify the impact of some modifications made in the clinical protocols. The following parameters were compared: indication and time under mechanical ventilation, surfactant administration, duration of oxygen therapy, types of ventilation support, daily care, rate of complications, length of hospitalization. The information was gathered and processed in the statistics analysis program EpiInfo 2007.

Results: There was a decrease in SDR severity, revealed by the decline in premature babies who required mechanical ventilation (64% in 2012 versus 51% in 2013), and the higher prevalence of non-invasive ventilation in 2013 (26% in 2012 versus 44% in 2013). Also, a decrease of the medium duration of ventilation was noticed (4.2 days versus 6.4 but not statistically significant p value = 0.059) and in oxygen therapy length (8.2 days versus 16.6, p=0.0022), also a decrease in severe brain hemorrhage 20% (n=16) versus 14% (n=19) p value = 0.087.

Conclusions: It is necessary to elaborate, upgrade and always follow the specific protocols for obstetrical and NICU departments in order to improve the neonatal outcome of preterm babies with GA lower than 34 weeks.

Key words: premature birth, premature, mechanical ventilation, oxygen therapy

Introduction

Premature births represent a great challenge for the obstetricians, as well as for the neonatologists. Neonatal respiratory distress syndrome represents one of the most acute pathology for finding the best strategy, in order to ensure survival and to decrease complications. These strategies begin before birth, continue in the delivery room and extend to the neonatal intensive care units.

In the last years, many of the treatment guides for the neonatal respiratory distress syndrome have been revised. A first revision was made in the year 2010[1] for the 2007[2] guide, and a second one was made at the end of 2012[3].

These reviews of the European consensus regarding the management of the neonatal respiratory distress syndrome have been a starting point for the updating of existing internal protocols in our clinic.

In 2013, the following protocols have been revised: antenatal care for premature birth risk pregnancies and premature rupture of membranes (≤34 weeks), stabilizing the premature babies in the delivery room, the early use of CPAP and non-invasive methods of ventilation support.

Furthermore, there have been substantial modifications of the nutritional support, through early enteral nutrition and decreased duration of parenteral nutrition. All these modifications have triggered the interest for a feedback on the impact regarding the evolution of the premature babies nursed in our clinic.

Material and method

The study has compared 243 of premature babies with the gestation age of ≤34 weeks, born in SCOG "Filantropia", between the years 2012-2013. The premature babies were split into two distinctive groups before and after the revised protocol : the ones born in 2012 (born - 93) were included in the P (-) group, and the ones born in 2013 (born = 150) were in the P (+) group.

The data was collected in a database and processed in the EpiInfo 7 statistics analysis.

At the beginning of 2013, modifications were made in the obstetrical protocols and in those operating in the neonatal intensive therapy department.

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Prenatal care protocol was updated to include all pregnancies with premature birth risk with gestation age between 24-34 weeks. During premature rupture of membranes, antibiotherapy will be initiated, and the period for tocolytic therapy will be 48 hours, a necessary time for making a complete corticosteroid course. The protocol for the premature birth risk pregnancies and PPROM is presented in table no. 1. If the spontaneous labor does not begin in 48 hours after the membranes rupture and/or after the corticosteroids cure, the attitude will be cesarian section.

In case of intact membranes, a short tocolytic treatment will be made, in order to allow the complete treatment with corticosteroids. If the delivery does not occur within 7 days after the corticosteroids treatment has finished, another treatment will not be applied.

Regarding the stabilization protocol of preterm babies in the delivery room the following modifications have been introduced, since 2012:

- warm diapers, bonnet, bootees, and plastic bags.
- delaying of umbilical cord clamping between 30 to 60 seconds (40 seconds on average)
- use of the lowest tolerated oxygen concentration by air/oxygen blender (30% on average) - the respiratory stabilization with positive pressure with a T piece (Neopuff) and mask.

Regarding the early treatment post-admission in the NICU department, the following therapies were applied:

- CPAP immediately after birth to all premature babies with high risk of respiratory distress (≤30 weeks) until the evaluation of their clinical status (PEEP ≥ 5 cm H2O)
- Intubation and ventilation for severe forms of respiratory distress and/or NCPAP failure. The synchronous modes of ventilation (SIMV) were preferred, with careful monitoring of the pressure/volume respiratory curves.

For the surfactant administration the recommendations from the European guidelines were usually respected:

- prophylactic in the first 15 minutes in the delivery room for GA < 26 weeks, or babies with GA ≤30 weeks, who require intubation.
- Therapeutical indication remained the same - the severe forms of respiratory distress.

The only change in therapeutic administration of surfactant was the case of RDS on NCPAP, with an oxygen concentration (FiO2)>50% and a pressure (PEEP) > 6-7 cm H2O. Sometimes we applied the INSURE procedure, followed by NCPAP.

For protocols of routine care the important changes were:

- A large amount of fluid would prevent the excessive weight loss.
- For hemodynamic stable newborns, early enteral nutrition in the first 24 hours and quick advancement will lead to a decreased use of central lines.
- Shorter antibiotherapy length (until the central line is removed) - Caffeine for premature apnea
- More restrictive transfusion protocols

Table no. 1 Protocol for pregnancies with high risk of premature birth and PPROM*

Gestation age	**Corticotherapy**	**Antibiotherapy**
24 – 27(+6 days) weeks	- Prenatal Corticotherapy - **Betamethassone - 2 doses of 12 mg at 24 hrs** **Dexamethsone - 4 doses of 8 mg at 12 hrs** - tocolytic** and conservatory expectative attitude (the pregnancy will be prolonged close to 34 weeks)	- antibiotic prophylaxis ab initio
28 – 33(+6 days) weeks	- prenatal corticotherapy - **Betamethassone - 2 doses of 12 mg at 24 hrs** **Dexamethsone - 4 doses of 8 mg at 12 hrs** - tocolytic** and conservatory expectative attitude	- antibiotic prophylaxis ab initio
34 – 36(+6 days) weeks	- Prenatal Corticotherapy is not needed	- intrapartum antibiotic prophylaxis in case of infection risk (eg. maternal infection proved with Streptococus B group)
All premature babies	- vaginal exam will be avoided - the delivery mode shall be decided between the obstetrician/neonatologist/mother - there will be a protective attitude, with an atraumatic labor as much as possible (without Oxiton)	

* PPROM – prolonged premature rupture of membranes

** tocolytic maximum 48 hours - the time necessary to complete the cortico- and antibioprophilaxy treatments

Results

This retrospective study enrolled 243 preterm babies, with gestation age <34 weeks. The data regarding the newborn, pregnancy and delivery are presented in table no. 2. Regarding demographic characteristics of the newborns, there are no significant differences (table no. 2). The average gestation period was 30 weeks for both studied groups (Fig. 1)

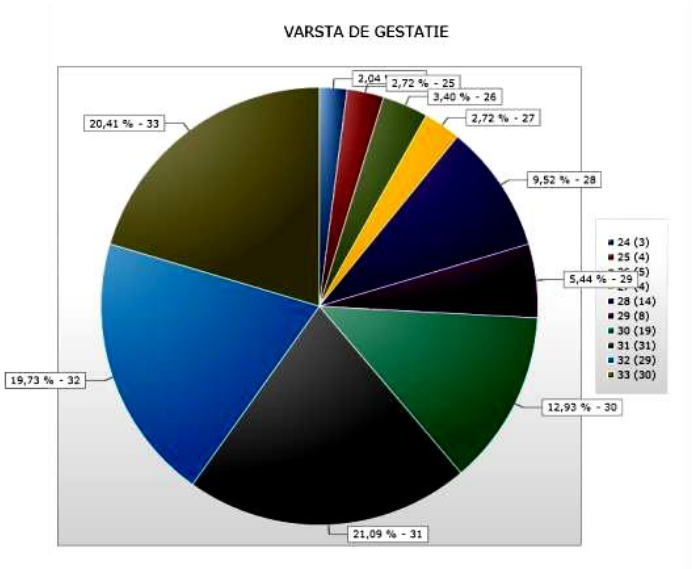

Figure. 1 The repartition according gestation age.

Table no. 2 Pregnancy and birth.

Variables	2012 P (+)	2013 P (-)	P value
No. of prenatal controls (average)	6	7.7	0.64
Corticosteroid prophylaxy	28,38% (23)	52,54% (64)	NS
Hours MR (average)	20.5 +/- 18.5	31.9 +/- 22.9	0.0187
Maternal-fetal infection	16% (14)	27% (38)	0,288021
Way of birth	Caesarian section 51%	65%	0.002
	Spontaneous 49%	35%	

Table no. 3 Demographic characteristics of newborns.

Variables	2012 P (+)	2013 P (-)	P value
Average GA	30.3+/- 2.4	30.4+/-2.2	0.85
Average GN	1501 +/- 459	1496 +/- 446	0.85
Sex M/F	53/47 %	52/48 %	NS

The time between the rupture of membranes and the moment of birth was higher in group P (+), average 31.9 +/- 22.9 hours versus 20.5+/-18.5; this increase is explained by the corticosteroid prophylaxis (p value = 0.0187).

Also, a significant difference can be noticed regarding the way of birth.

In group P (+) the incidence of caesarian section was increased, due to a lack of spontaneous labor in case of PPROM (65% versus 51% p value = 0.002).

In group P (+) the incidence of maternal-fetal infection was higher (16% versus 27%), unrelated to the period of ruptured membranes labor (P-value = 0,90699), possibly due to antibiotics prophylaxis, a standard for all pregnant women with PPROM.

Respiratory distress syndrome was equal in both groups, with less severity in group P(+). In 2013, the percentage of ventilated premature babies was smaller (15% versus 64%) and the non-invasive ventilation mode was predominant (NCPAP used in 44% of the cases with respiratory distress versus 26% in 2012).

The average of ventilation time in group P(+) was 4.2 days versus 6.4 (p value = 0.059), while the length of oxygen therapy was reduced by half: 8.2 days versus 16.6 (p value 0.022) (table no. 4).

By applying the linear regression between more variables (table no. 5), it seems the corticosteroid prophylaxis, the gestation age and the surfactant have significantly influenced the time of oxygen therapy in both groups (Correlation Coefficient: r^2= 0,33). Because no significant differences were observed for gestation age and surfactant administration between the two groups, the prenatal corticosteroids prophylaxis seemed to be the most important variable which influenced the severity of respiratory distress, as well, the time of oxygenotherapy.

The treatment, the evolution and the complications between the 2 groups are presented in the table no. 6.

Table no. 4 Newborns characteristics.

Variables	2012	2013	P value
Apgar score at 5 min	6.6	6.9	0.055
Pulmonary stabilization with Infant T-Piece Resuscitator (Neopuff)	56% (51)	65% (95)	NS
SDR	72% (69)	74% (108)	0.67
VM	64% (58)	51% (75)	0.023
NCPAP	26%(11)	44% (40)	NS
Surfactant	19.5% (18)	21.8% (30)	NS
Average time of mechanical ventilation	6.4	4.2	0.059
Average time of oxygenotherapy	16.6	8.2	0.0022

Table no. 5 Corelation between the ventilation time and other variables (linear regresion).

Variables	Std Error	F-test	P-Value
CORTICOSTEROIDS	1,036	4,1059	0,045396
MATERNAL-FETAL INFECTION	1,093	0,1218	0,727800
GA	0,223	6,2918	0,013738
DISTRESS CAUSE	5,706	0,0211	0,884799
SURFACTANT	1,039	7,5790	0,007014
VENTILATION TYPE (HFOV + SIMV/NCPAP/HFOV)	5,988	0,0576	0,810786
CONSTANT	8,904	6,3036	0,013652

Table no. 6 The outcome of premature babies from the two groups/Current care.

Variables	2012	2013	P value
Caffeine treatment of apnea spells	8,82% (3)	75,51% (37)	0,0130685
PRBC transfusions % Mean	34% (3,8 +/- 2,8650)	25% (1.6+/-0,9554)	0,0019
Nosocomial Infection	13% (12)	5.6% (8)	0.89
HIV Incidence	20% (16)	14% (19)	0.087
ROP Incidence	27% (23)	26% (37)	0.09
Weight at 14 days	1394+/-425	1547+/-420	0.0235

Calories at 14 days cal/kg/day	106 +/-26	112 +/-17	0.8
APT duration	5.2	1.7.	0.001
Start of enteral nutrition	4.2	2.2	0.003
Length of CVC (average)	13,7+/-12,5	8,1+/-3,4	0,000412
Length of hospitalization	37	34	0,505272
Death	14% (13)	7% (10)	NS

The frequency of apnea spells was allmost equal between the two groups 33% (29) versus 35% (29). In 2012, 75% of apnea spells were treated with Aminophylline, unlike 2013 when it was replaced with Caffeine Citrate. Also, caffeine was used in premature babies in NCPAP and, generally, for all premature babies with apnea attacks and gestation age under 30 weeks.

The mean of treatment was 7 days (minimum 1 day - maximum 46 days).

Concerning transfusional therapy in P(+) group there was a significant decrease, 25% versus 34% and the mean of transfusions/child was 1.6+/-0,9 versus 3,8 +/- 2,8 , p value = 0,0019. This can be explained by more restrictive transfusion protocols which combine clinical perception, respiratory therapy, postnatal age and less the "target value" of haemoglobin/haematocrit.

The enteral nutrition was started earlier for group P (+), usually in the second day of life (2.2 versus 4.2 days), with a better caloric input at 14 days (112 +/- 17 cal/kg/day vs. 106 +/- 26 cal/kg/day) and with a better weight gain in the 14th day of life: 1547 +/- 420g vs. 1394 +/- 425g, p value=0.0235. This determined a decrease of total parenteral nutrition (8.1 days versus 13.7 days). The enteral nutrition was made only with fortified maternal milk.

There were no significant differences concerning cerebral hemorrhage (20% versus 14%), but there was a lower proportion of intraventricular hemorrhage of the 3rd and 4th degree in group P(+) (5 children versus 11 children). The average hospitalization time was equal for both groups (35 days) and the death rate was half in the P(+) group 7% versus 14%.

Discussions

There is an European consensus of the guidelines regarding the management of the neonatal respiratory distress syndrome elaborated by a group of experts in neonatology.

They have analyzed the guidelines from 2007 and 2010. In 2013 they made an guideline update based on published studies until the end of 2012.

There are strong evidence for the benefits of corticosteroids prophylaxis in preventing SDR.

The premature birth can be avoided in case of PPROM by using antibiotics and tocolytics for a short period of time, which allows the pregnant woman to be transferred to a perinatal center and to complete the corticosteroids treatment. [4]

Prenatal corticosteroids prophylaxis in women with a high risk of premature delivery, reduces the risk of neonatal death (relative risk 0.55;95 % CI, 0.43-0.72), and by using a single course there are significant less side effects for the mother or the fetus.[5]

Prenatal corticosteroids prophylaxis decreases the risk of intraventricular hemorrhage and NEC[5]. It is recommended in all high risk premature deliveries-under 34 weeks of gestation

Once the corticotherapy is started, the best time for delivery, is between 24 hours and seven days[5]. After 14 days from corticotherapy, steroids benefic input decreases[6] and another course might influence the fetal growth. [7]

Many studies confirm the positive aspect of delayed umbilical cord clamping (30-60 seconds) for premature babies. [8] Almost half of the blood volume of the premature babies can be found in the placenta and by delaying the umbilical cord clamping, the blood volume increases, especially after vaginal delivery. A meta-analysis of 50 studies regarding the delay of umbilical cord clamping in preterms showed that this procedure increases the hematocrit, leads to fewer transfusions, less incidence of NEC and a decrease nearly to 50% of IVH.[9]

The actual protocols suggest the use of a lower oxygen concentration in the delivery room, so that the saturation corresponds to normal values in transitional period. During the transitional period, the saturation measured through pulse-oximetry at the right hand has to gradually increase from 60% to 80% in the first 5 minutes and up to 85% after 10 minutes.[10]

By using early NCPAP with positive pressure control we can stabilize the preterms better after birth, and reduce the need for mechanical ventilation and for surfactant

therapy.[11-12] Infant T-Piece Resuscitator (NeoPuff) measures the inspiratory pressure. The non-invasive respiratory support is defined as any form of ventilation support which is not given through endotracheal tube. Here CPAP, different types of nasal prongs or mask (NIPPV) and oxygen administrated through the high-flow cannulae are included.[13] The sooner it is applied, after birth, the better the chances are to avoid mechanical ventilation and surfactant therapy.

Methylxanthines drugs had been used for a long time in the treatment of prematurity apnea and in order to allow the extubation from mechanical ventilation.

The long term effect of caffeine in apnea of prematurity (CAP) was analyzed in 2006 children with birthweight <1250 g, that received randomized caffeine and a placebo treatment in the first ten days after birth. In children who received caffeine the ventilation was stopped one week before the ones who received the placebo treatment, with a significant decrease of BPD.[14] Monitoring them at 18 months has shown a better evolution for the children treated with caffeine, with lower death rates and neuro-disorders (brain paralysis or slow cognitive).[15]

Regarding routine care in the two groups, several differences regarding fluids and nutritive aportwere noticed. In the delivery rooms, the heating was made by using thermal radiant, warm diapers, bonnets and bootees.

A plastic bag was rarely used for children under 1000g.

In the neonatal intensive care unit, the temperature control was provided by incubators (set temperature 36,5 C, humidity 60 – 70%), in order to decrease the water loss.[16,17]

The fluid aport varied according to the gestational age, weight, and pathology. In the first 24 hours, the fluid volumes varied from 80 – 100 ml/kg in the P (+) group {60 – 80 ml P (-)},with an increase of fluid according to diuresis, weight variations, plasma electrolytes level (especially Na).

There was no increase in the PDA and NEC incidence.[18]

We tried a parenteral nutrition with a protein input ≥ 1 g/kg/day from day one for a faster growth 1g/day until 3,5 g/day. This protein input prevents the negative balance, by increasing the protein synthesis and the nitrogen retention which stimulates the weight growth[19-22].

Carbohydrates ratio in the first 24 hours was 4-5 mg/kg/min, with a daily increase of 1-2 mg/kg/min based on glycemia. We have usually avoided the use of lipids in parenteral nutrition, if the enteral nutrition was initiated in the first 48 hours. The lipids were introduced in the parenteral nutrition if the enteral nutrition was postponed >48 hours, because of cardio-circulatory instability or digestive pathology (NEC). The parenteral nutrition was usually administrated through central lines.

The enteral nutrition was initiated as early as possible (2,2 days on average), and, usually, as soon as there was a cardio-circulatory stability (tisular perfusion and blood pressure at normal values for the age, even with with inotrop support <10 mcg/kg/min).

The start rate was 10 – 20 ml/kg/day using maternal milk, and increasing the rate even in the same day.

The Cochrane studies have shown that there is no NEC risk with an early nutrition and with the fast advancement of it.[23-25].

Conclusions

The protocols for each department are essential, but they have to be in accordance with the recommendations of the european consensus guidelines on the management of neonatal respiratory distress syndrome. Because the latest recommendations are based on clinical studies performed in the last years, the implementing of these protocols greatly improves the outcome of premature babies with respiratory distress syndrome.

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THE DYNAMIC OF OBESITY EPIDEMIOLOGY AND RISK FACTORS INVOLVED IN THE DEVELOPMENT OF CHILD OBESITY IN A GROUP OF CHILDREN FROM TIMIS COUNTY

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Abstract

Child obesity is a multifactorial disease. At present, prevention is the most effective approach. Aim: To determine the dynamic of overweight and obesity and the presence of some of the already known risk factors. Material and Methods: The retrospective study was performed in IInd Clinic of Pediatrics, Timisoara for a 3 year period. The study group included 174 children, 88 boys and 86 girls, with a mean age 11.87 +/- 3.33 years, evaluated for excessive weight. The first evaluation included complete personal and medical history, and complete physical exam including anthropometric indexes and specific biochemical tests. Results and discussions: Out of the study children 8.05% were overweight, 40.23% had mild and moderate obesity, and 51.72 % had severe obesity. The majority (71.83%) of cases were from urban areas. Positive family history of obesity was seen in 31.03% (n = 54) of children. More than half of these children, (62.96%) were severely obese. A small percent (15.73%) were SGA or LGA. 74.84% were naturally born and only 25.16% by caesarean section. More than half of the obese children, (55.08%) were breastfed for one or two months or fed with formula or cow milk from the beginning. Conclusion: Positive family history for obesity is a strong predictor for child obesity. Mode of delivery, birth weight, breastfeeding are also involved in child obesity development but evaluated separately seem to play less important roles.

Key words: child obesity, risk factors, family history, birth weight, breastfeeding.

Introduction

Child obesity remains an important pediatric problem. There is no unanimity regarding the most effective treatment, so prevention is still the most important approach. It is well known that obesity is the result of interaction between multiple environmental and genetic factors.

Identification of children at high risk of obesity is challenging, and the data on this subject in Romania are scarce. Numerous risk factors have been recognized to be involved in the onset and development of childhood obesity. Family history of obesity has been shown to be one of the main predictors for child obesity (1, 2), not only for the genetic component, but also for the environmental ones like eating habits and pattern, perception on child obesity. Another important group of related childhood obesity risk factors are those concerning the birth (birth weight and delivery by caesarean section or vaginally) and the first year of life. The World Health Organization recommends exclusive breastfeeding for the first six months of life and the introduction of complementary food in children after six months. It also recommends that partial breastfeeding continue up to two years of old (3).

The aim of this study was to establish the dynamic of the obesity epidemiology in a geographic region and the relationship between family history of obesity, mode of delivery, birth weight, breastfeeding, the introduction of new complementary food before six months of age and child obesity.

Material and methods

The retrospective study took place in IInd Clinic of Pediatrics, County Clinical Emergency Hospital "Pius Branzeu" Timisoara between 1st January 2010 and 31st December 2012. The study group was formed of 174 children, ranging from 3.5 to 19.1 years old, which were evaluated for excessive weight. The first evaluation included a complete personal and medical history, complete physical exam including anthropometric indexes and specific biochemical tests. The children were measured without shoes, wearing light outdoor clothes. Height was measured using a rigid stadiometer to the nearest 0.1 centimetre, and weight using a calibrated electronic scale to the nearest 0.5 kilograms. Two different measurements were performed, and the mean was recorded. The 2007 WHO growth standards were used for diagnosis and classification of obesity. Overweight was defined as a BMI z-score above 1SD but lower than 2 SD, mild and moderate obesity defined as a BMI z-score between 2 SD and 3 SD and severe obesity when BMI z-score was over 3 SD.

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Former small for gestational age (SGA) was defined by birth weight below the 10th percentile for gestational age and sex, while large for gestational age (LGA) was defined as above 90th percentile for gestational age and sex, according to WHO growth standards. All children with birth weight in between these limits were considered appropriate for gestational age. Children born before 37 weeks of gestation were excluded from the initial study group. The analysis included the following variables: family history, birth weight, birth by caesarean section or vaginal, breastfeeding, breastfeeding duration. Quantitative data with normal distribution were presented as mean +/- standard deviation (SD).

Results and discussion

From the initial study group (n = 174), 37.93% of children were evaluated in the first year, 25.86% were evaluated in the second year and 36.20% in the third year. This study results were different from the ones found in another Romanian study (4). We found no increase in the annual incidence of obesity. Moreover, a slight decrease in the number of patients addressing the clinic during the second year. The both studies had significant limitations: the relatively small number of subjects included and, maybe the most important is the children selection. All children addressing for excessive weight were included. So these results do not represent the prevalence and incidence of child obesity. It can rather be an indicator of recognizing the problem, being informed and searching for medical help.

Most of the cases were from urban areas (71.83%), and the sex ratio male was approximately 1:1 (88M: 86F), and the mean age was 11.87 +/- 3.33 years. Children were divided into four age groups: under 7 years; from 7.1 to 10 years; from 10.1 to 14 years and above 14.1 years old. The incidence by age group and sex is shown by years in Figure 1. The highest incidence of obesity was seen in the third year of study in the 10.1 to 14 years group, 39.08% (n = 68).

Using BMI 2007 WHO criteria and growth standards for age and sex, the study group was divided into three groups: A: overweight (n = 14: 13 F and 1 B) – 8.05%; B: mild and moderate obesity (n = 70: 38 F and 32 B) – 40.23%; and C: severe obesity (n = 90: 35 F and 55B) – 51.72 %. It is thus alarming that more than half of the evaluated children came to the doctor only when they were severely obese, and just a small number (under 10%) when the weight problems began.

It is known that family history is a significant predictor for child obesity and children with one obese progenitor had four times (1) higher risk to have weight problems (5,6). It seems that BMI during infancy was more strongly associated with maternal than paternal obesity overall (7). Analyzing the family history was showed that 31.03% (n = 54) of children had at least one overweight or obese parent or grandparent. More than half of these children (62.96%) were severely obese. Correlating these data with the age of the child, it was found that the number of children with positive family history was higher in the 7.1 to 10 years of age group (43.58%), followed by the group of children aged under 7 (33%). Heredity, therefore, may play an important role during the first years of life, but up to prepuberty and during puberty and adolescence this role is taken by other factors such as nutritional habits, hormonal changes and so on. These results are similar with the ones published by Cosoveanu S. and al. (8) in which 21% of overweight and 23% of obese kindergarten children had one obese parent, while 6% and 9% respectively had both parents obese. When analyzing the primary school children, in the same study, 12% of overweight and 32% of obese children had one obese parent, while 11% and 9% had both parents obese. A smaller percent was found in another Romanian study (9) in which only 10% had a positive history of obesity. The authors concluded that the prevalence of obesity is increasing by approximately three times in children with positive family history of obesity.

Birth weight it is considered to be a risk factor as well. Twelve children from the initial study group were excluded because of the lack of information on pregnancy evolution, type of delivery, birth weight and length. Another three cases were excluded because of low birth weight due to prematurity. Hence, the new study group has been divided into three subgroups using this variable: SGA (n = 8), AGA (n = 134) meaning 84.27% and LGA (n=17) – Figure 2. Therefore, a small percent (15.73%) of overweight and obese children were SGA or LGA. Some studies have found that there is a linear relationship between birth weight and childhood obesity (10, 11). One of these studies suggested the use of ponderal index as a predictor of later adiposity rather than just the use of birth weight (11). The direct relationship between birth weight and fat distribution during childhood seems to be influenced by parental weight. Lower birth weight is more frequent associated with central adiposity among children of overweight parents. Among children, with normal weight parents, there was a significant association only for birth weight and later subscapular skinfold, but this association was less significant compared to the parents group with excess weight (12).

Another risk factor is the mode of delivery. The mechanism underlying this association is unknown. There are a few theories: one is related to the different intestinal flora in children born naturally versus those borne with caesarean, other are related to effects on inflammation, immune and endocrine function. So, 74.84% of children were born vaginally and only 25.16% were borne by caesarean section. These percentages might not be accurate as in the last 5 years the number of on demand caesareans alarmingly increased. In a 3 years prospective study Huh et al. concluded that birth by caesarean section is associated with two-fold higher odds of obesity at three years of age (13). In another smaller Chinese study, the children born by caesarean had five times (OR = 5.23) higher risk of becoming obese.

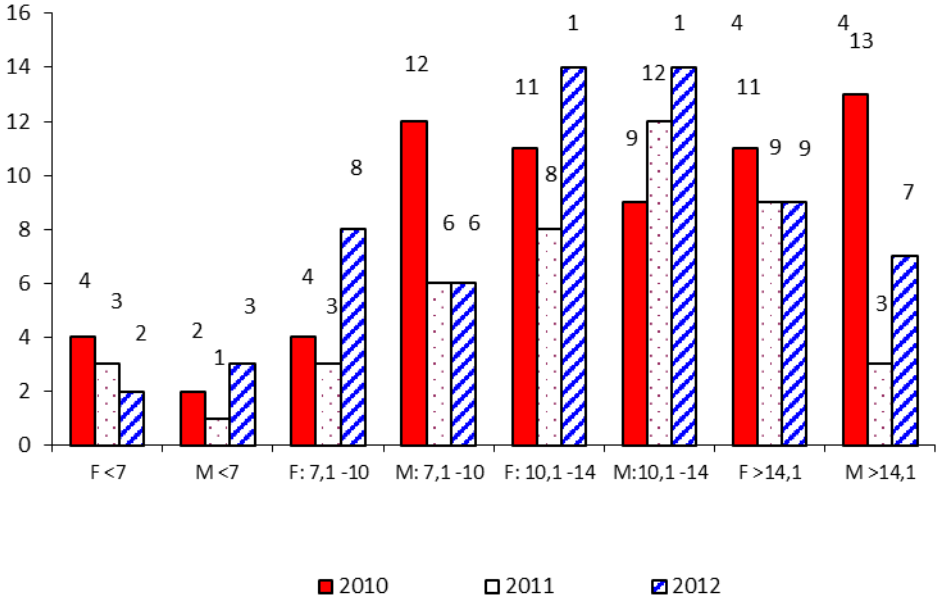

Fig.1. Incidence of overweight and obesity in the study group by age, sex and year of diagnosis.

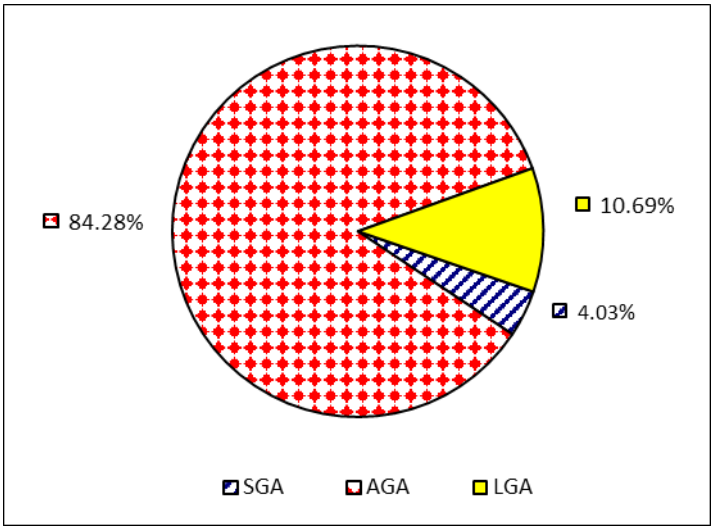

Fig.2. Study group distribution by birth weight.

Breastfeeding is known to be a protective factor, but optimal duration of breastfeeding is uncertain. Five children from the original group were excluded because the data were scarce. The children were divided by the period of breastfeeding in six groups. The first group was formed by children fed with formula or cow milk = 47 (28.11%). The second comprised those breastfed under one month = 27; the third: children breastfed between one and two months = 18; the fourth group - those breastfed for three to four months = 30; the fifth, children breastfed five to ten months = 22 (13.17%) and, the sixth group included children breastfed over ten months = 23 (13.77%). More than half of the obese children (55.08%) were shown to have been breastfed for one or two months only or fed from the beginning with formula or cow milk. The results were similar with the ones published by Mindru et al. (4). The authors found that 33% of the children were never breastfed and only 11.64% of the study group children were breastfed for five to ten months. The duration of breastfeeding remains an important risk factor. In a study by Huus et al. (15), who analyzed data from birth and later, at 5 years, it was shown that children who had been exclusively breastfed for more than 4 months were less likely to be considered obese (OR: 0.82) compared with those who were exclusively breastfed for less than 4 months. In an English birth cohort study (16) it was observed that the odds ratio of weight excess was 1.14 among children breastfed for ≥ 6 months compared with those who had never been breastfed. The benefits of breastfeeding are not only represented by the high quality of maternal milk but also by the development of protective behavioral mechanisms (e.g. better self regulation in the energy intake).

There were insufficient data concerning the timing and order of introduction of solid foods to diet, but most of the parents began the diversification at four months or earlier and, mistakes like introduction of wheat products before six months of age or of sweets, in the first year of life were frequent.

Conclusions

More than half of the evaluated children presented severe obesity (51.72%).

Prevention remains the most effective way in fighting obesity epidemic, so early recognition of the risk factors is crucial.

Positive family history of obesity is a strong predictor for child obesity.

Mode of delivery, birth weight, and breastfeeding are also involved in the development of child obesity. When evaluated independently, all the three factors seem to play less important roles.

However, informing the future parents about the advantages and disadvantages of the decisions they make within the first year of their children's life may help preventing obesity and all the medical and social complications that are coming along with it.

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DOUBLE ILEO-ILEAL INTUSSUSCEPTION CAUSED BY MESENTERIC LYMPHADENITIS ASSOCIATED WITH MULTIRESISTANT STAPHYLOCOCUS EPIDERMIDIS PERITONEAL INFECTION

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Abstract

In intussusceptions one segment of the bowel (the intussusceptum) passes onwards inside the adjacent distal bowel (the intussuscipiens). The apex of the intussusceptum is termed the lead point. Once this telescoping phenomenon becomes established, intestinal obstruction follows. Ileocolic intussusception represents one of the more common surgical emergencies in the first 2 years of life, the peak incidence is in infants 5-9 month old. However ileo-ileal intussusception is rare and occurs in older children or infants less than 3 month of age. It is usually associated with other medical conditions (Henoch-Schönlein purpura, cystic fibrosis, hematologic dyscrasias) and occasionally occurs after major abdominal surgery.We present the case of a 4 year old boy with a double ileo-cecal intussusception with mesenteric lymphadenitis as a lead point, associated with multiresistant Staphylococcus epidermidis peritoneal infection. This case highlights the use of ultrasound in diagnosing this pathology and how helpful it can be in diagnosing the cause of small bowel obstruction in children.

Key words: ileoileal intussusception, ultrasound, multiresistant Staphylococcus

Introduction

Colicky abdominal pain, with or without vomiting, is seen often in infants and in most instances does not reflect significant pathology (colic of infancy, constipation). A serious cause of colic is however intussusception. In intussusception, one segment of the bowel (the intussusceptum) passes onwards inside the adjacent distal bowel (the intussuscipiens). The apex of the intussusceptum is termed the lead point. Once this telescoping phenomenon becomes established, intestinal obstruction follows.

Intussusception may be idiopathic or secondary to a lead point (2-12% of infants and children with intussusception). This is seen most commonly in infants younger than 3 months or older than 5 years of age. The lead points include Meckel's diverticulum, enlarged mesenteric lymph nodes, benign or malignant tumors of the mesentery or the intestine, mesenteric or duplication cyst, ectopic pancreatic and gastric rests, inverted appendiceal stumps, intestinal hematomas secondary to abdominal trauma, submucosal hematomas, intestinal hemangioma, Kaposi sarcoma, posttransplantation lymphoptroliferative disorders. Intussusception can also be classified according to site: over 90% of patients have a ileo-colic or ileo-ileo-colic intussusception, enteroenteral intussusception is rare (between 1-8 % of all childhood intussuceptions).

Case report

A 4 year old boy was presented by his parents at the emergency department of our hospital with a history of 24 hours of colicky abdominal pain and vomiting. The vomiting was described as initial nonbilious and then bilious. The last bowel movement was the day before. There was no significant patient history of preexisting illness. From the anamnesis we found out that he had an upper respiratory tract infection 2 weeks before, treated at his family doctor's office.

At examination the patient was very anxious. The local exam revealed a normal shape of the abdomen, with periumbilical tenderness at palpation and no signs of peritoneal irritation. Rectal examination was normal.

The abdominal X-ray did not reveal any air-fluid levels as sign of intestinal obstruction.There was a paucity of gas in the lower abdomen.An ultrasound examination revealed however images that were suggestive for a small bowel obstruction caused by intussusceptio

The patient underwent emergency laparatomy. When opening the peritoneal cavity a small amount of serous fluid was found. A sample of this fluid was sent for microbiology examination and culture. Two small bowel intussuceptions where found at operation. These where reduced and the bowel did not show any signs of necrosis. Mesenteric adenopathy was found to be the lead point of intussusceptions. No Meckel's diverticulum or other anomalies were found. A tactical appendectomy was performed. The postoperative course was uneventful. The patient received antibiotherapy with Piperacillin-Tazobactam. The microbiology examination of the peritoneal fluid revealed an infection with multiresistant Staphylococcus epidermidis for which therapy with Linezolid was started (iv and afterwards syrup per os). The patient was released from the hospital on the 7th postoperative day. A follow-up visit showed good healing of the surgical wound and no postoperative problems.

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Discussion

Intestinal intussusception is the most common cause of intestinal obstruction in early childhood. It is an abdominal emergency.

The debut is usually acute. Clinical signs include a triad of symptoms, including vomiting, abdominal pain and passage of blood per rectum or currant jelly stools. The vomiting is usually nonbilious to start with, but when intestinal obstruction occurs it becomes bilious. As the condition progresses the infant develops additional symptoms, including those associated with shock, such as paleness, lethargy and fever.

The diagnosis of intussuception can be very difficult in the early stages, as it may mimic other diseases, for example commun mesenteric lymphadenitis. A mass may be palpable in the right hypochondrium in the case of an ileo-colic or ileo-ileo-colic intussuception, but is hard to detect and is best palpated between spasms of colic, when the infant is quiet. The rectum abdominis muscle is also an obstacle, which can hide the abdominal mass and make it hard to palpate. In case of an ileo-ileal intussuception the mass is also very difficult to palpate and can be periumbilical. Rarely the mass may prolapse through the anal canal, usually the intussuception is self limited at the level of the transverse colon, because of the length of the mesenterium. The rectal examination is therefore very important and can reveal the typical currant jelly stool in advanced intussusception, also one can sometimes palpate the mass (rare cases). Abdominal distension becomes apparent clinically when the obstruction becomes complete.

Plain abdominal radiographs reveal signs that suggest intussusception in only 60 % of cases. They may be normal in early stages of intussusceptions. Many authors seem to agree that the plain abdominal radiograph is unsafe(1,2,3,4,5,6,7,8,9,10,11). A very interesting study was performed by Eklof and Hartelius (12) which concluded that the hallmarks of the condition were scant abdominal gas in 89% of cases, this abnormal appearance augmented by scanty faecal content in 82%, with an abscure abdominal mass lesion in 62% of patients.

As the disease progresses, the earliest radiographic signs include an absence of air in the right lower and upper quadrants and a right upper quadrant soft tissue density which is present in 25–60 % of patients.These findings are followed by features of small bowel obstruction, with dilatation and air-fluid levels in the small intestines (13).

However ultrasonography is the main stay of diagnosing intussusception with an overall sensitivity and specificity of 97.9 and 97.8 %, respectively. Ultrasonography should be the first examination in those patients with suspected intussusception. The ultrasonographic signs of intussusception include the target and pseudokidney signs as well as dilated bowel loops (14). Enlarged ovoid hypoechoic mesenteric lymph nodes of more than 4 mm in short axis are usually found in the invaginated mesentery or mesocolon, mainly at the invagination neck.

Sonographic detection of a small-bowel intussusception is more difficult than for the usual ileocolic form. The intussusceptions may be found deep in the abdomen surrounded and obscured by air-filled or fluid-filled dilated loops because of the associated small-bowel obstruction (15, 16, 17). Therefore, a graded and patient compression of the entire peritoneal cavity is mandatory. The only diagnostic feature of the anatomic type is a topographic one. Indeed, ultrasound always reveals a normal location of the ileocecal valve and colon. The lesions may be found in the paraumbilical or in the left abdominal regions (17). Kornecki et al. (14) found that small bowel intussusception was characterized on the sonogram by a smaller target lesion (2–3 cm) and was more commonly found in the paraumbilical or left abdominal regions. This is in concordance with the findings in the presented case.

In the case of the presented patient ultrasonography was diagnostic. Bartocci et al (2008) (15) found that ultrasonography showed great accuracy and sensibility in the diagnosis of intussusception. It can add important elements that the physicians can use to make the right choice of treatment. Moreover sonography is affirming as a safe guidance tool, in place of fluoroscopy, for hydrostatic or pneumatic nonsurgical reduction of children's intussusception.

Non-operative reduction is now considered by almost all paediatric emergency units as the method of choice for its treatment. The benefits to the patient of non operative reduction rather than surgery have been well documented. The discomfort to the patient of post operative pain and the risk of subsequent adhesive bowel obstruction occur only in those treated by laparotomy. In addition there are a number of other factors that represent significant morbidity. Nevertheless, patients with successful reduction have usually to be carefully observed in order to detect early recurrences and infectious complications. Tolerance of a normal diet is evaluated under medical control.

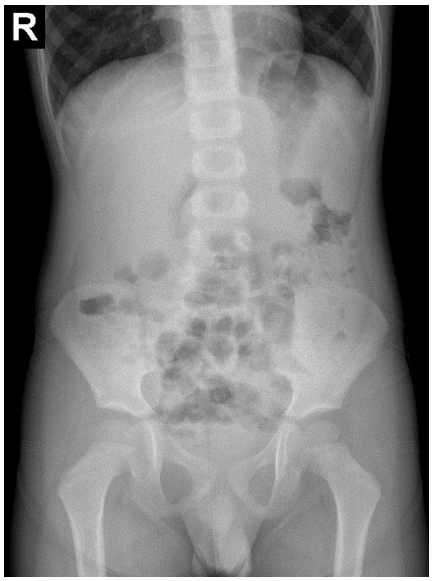

Fig. 1. X-ray of the abdomen.

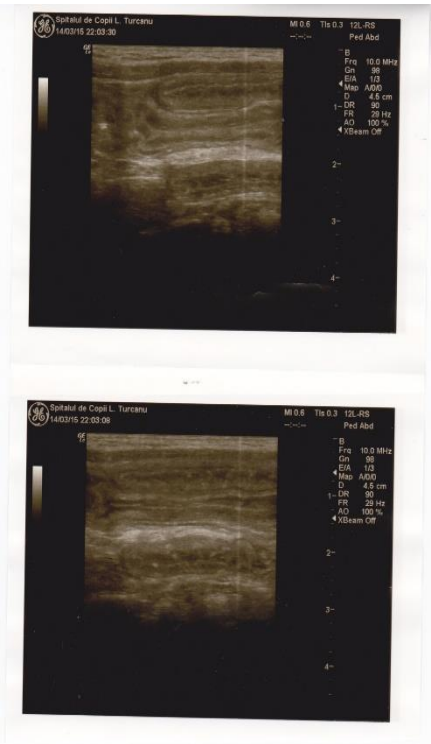

Fig. 2. Ultrasound of the abdomen, showing intussusceptions (longitudinal section). There seemed to be two intussusceptions at different levels of the small bowel.

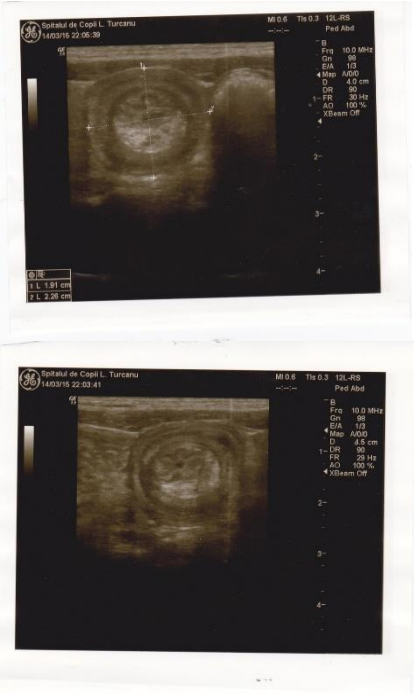

Fig. 3. Ultrasound of the abdomen, showing intussusceptions (transverse section). The positions of the intussusceptions where left paraumbilical and one of them was eventually palpable. A Doppler examination revealed an adequate perfusion to the affected gut

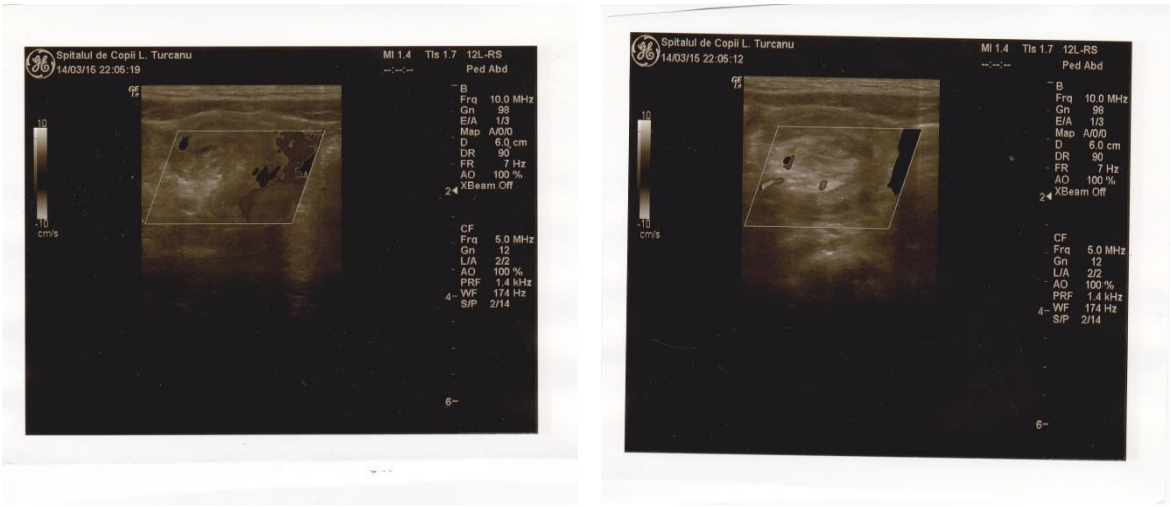

Fig.4. Doppler ultrasound of the intussusceptions showing adequate perfusion.

However in case of an ileo-ileal intussusception non-operative reduction is hard or impossible to obtain and some authors consider therefore that it is of no value in such a case.

Sometimes it is very hard to differentiate a small bowel intussusception from an ileo-colic one. Wiersma et al. (19) stated that small bowel intussusceptions (SBI) are usually shorther than ileo-colic ones.

In a study by Ko et al (20) the accuracy of sonography for detecting SBI in pediatric patients was 76.5%. The transverse diameter of the SBI lesions and the thickness of the outer sonolucent rim measured on sonograms had no predictive value for the presence of bowel complications. Blood flow detected on color Doppler sonography has been reported as an indicator of bowel viability (20).

In the case of SBI one must think of a possible lead point like a Meckel's diverticulum, myoephitelial hamartoma, heterotopic pancreatic tissue, mesenteric lymphadenitis, Kaposi sarcoma,Peutz-Jeghers syndrome etc, or other diseases like volvulus or perforated appendicitis (21,22,23,24,25,26). In a study by Newman et.al. (27) the authors stated that hat ruptured appendicitis can appear as a rounded, mass-like structure with multiple rings that can be easily mistaken for intussusception. Awareness of the possibility of this confusion should encourage more detailed, thoughtful scrutiny of the initial images, with a greater consideration of the possibility of complicated appendicitis. Particular attention should be paid to evaluating the presence of surrounding inflamed fat in appendicitis and intralesional hypoechoic lymph nodes in ileocolic intussusceptions. In situations where ultrasound or enema findings are unusual or at odds with the clinical picture, radiation concerns should not prevent the appropriate move to CT for clarification. MR is being used more commonly for the diagnosis of acute appendicitis and might also be an appropriate alternative in suitable patients. The CT scans obtained in the study by Newman et al (27) were diagnostic of ruptured appendicitis with no confusion with intussusceptions. CT can also be helpful in diagnosing associations of intussusception and other diseases, for example volvulus (22).

The treatment of ileoileal intussusceptions is surgical reduction with or without bowel resection. A small bowel intussusceptions can sometimes have a spontaneous reduction (28, 29).

Transient small bowel intssusceptions are short-segmented, self limited and without a leadpoint They are only transient phenomena and should be called benign small bowel intussusceptions (BSBI) (Doi et al. 2004) (29).They are usually found incidentally in asymptomatic patients or in children presenting with abdominal pain. They have no clinical significance because, in most of cases, direct correlation of symptoms to ultrsonografic findings is absent or questionable (30). The high rate of patients with BSBI actually observed may be related to increased use of abdominal ultrsonography in children and improved image resolution and quality (30). Siaplaouras et al. (2003) (31) have reported that BSBI was frequently associated with lymphoid hyperplasia at ultrasonography. The frequency and number of BSBI are also increased in patients with celiac disease (31).

There have also been reports of patients with small bowel intussusception which have been treated conservatively (32).

Conclusions

In most cases of small bowel intussusception, surgery should not be delayed because of the high incidence of a leadpoint and also the need to obviate small bowel ischemic necrosis. The procedure consists of reduction of the intussusception alone or of intestinal resection for bowel necrosis and/or for a leadpoint with a termino-terminal anastomosis. In Burkitt lymphoma, surgery may be required either for the histological diagnosis of a localized tumor or for the treatment of an intussusception with bowel compromise. In the last years laparoscopy has proven to be a valuable method in treating small bowel intussusception since it provides a less invasive alternative and it might be expected to reduce the post-operative hospital time (33).

In a study by Yao et al.(34) based on statistical analyses of 316 operated cases among 5537 pediatric intussusception patients they found that female sex, length of history and ileo-ileal intussusception are the risk factors for loss of intestine viability.

Children with ileo-ileal intussusception are more endangered than those with other intussusception types for developing intussusception-associated loss of intestine viability. The reason might be that the early symptoms of ileo-ileal intussusception cases were mild and not typical, which might lead to the delay in diagnosis and treatment. Ko et al. (20) also indicated that pediatric small bowel intussusceptions typically presented with nonspecific clinical abdominal symptoms that sometimes led to delays in seeking appropriate medical care and further complications.

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THE GENETIC CAUSES OF CHEST WALL MALFORMATIONS

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Abstract

Introduction. The sternum, a long, narrow flat bonne, has an important structural and functional role in the human body. It has an important role in body structure and function. Sternal malformations are relatively frequent isolated or as part of some genetic syndromes. Pectus excavatum (PE) and pectus carinatum (PC) represent more than 95% of sternum malformations. Objectives. The study aims to highlight the genetic origin of the most common congenital sternum abnormalities (PE and PC) and the role of specific genes in the appearance of those deformities. The etiology of all congenital sternum abnormalities is not clearly identified yet. Material and Methods. We reviewed the online data bases and specific journals archives. The titles and abstracts of studies were evaluated by all the authors independently. For eligible studies, at least one review author extracted the data. We excluded studies who present the management, the treatment or any other different information by the genetic part of the targeted pathology. We also excluded the studies that presented syndromic PE patients. Results. We detected 402 possible eligible studies and after the evaluation according to the inclusion criteria 392 were excluded. Excluded causes were presented in methods section. From the included studies, 8 studies present genes involved in PE appearance, 1 study for PC appearance and 1 study for pectus deformity. Discussions. We included studies that demonstrated the inheritances of PE without emphasize the involved genes and also two studies with syndromic PE but with a new genetic cause. Conclusions. All the described studies sustain the genetic origin of PE and PC. It has large limits that make almost impossible in this moment to estimate a precise contribution of genetic factors in congenital sternum abnormalities. We need more studies with large cohorts to prove the prevalence of genetic factors in PE.

Key words: chest wall malformations, Pectus Excavatum, Pectus Carinatum, genetics

Introduction

The sternum, a long, narrow flat bonne, has an important structural and functional role in the human body. It stabilizes the body skeleton, it is involved in the movement of arms, neck and head and it also protects some vital organs like the heart, the aorta, the timus gland. Sternal malformations (pectus excavatum, pectus carinatum, cleft sternum, pentalogy of Cantrell, asphyxiating thoracic dystrophy, and spondylothoracic dysplasia) are relatively frequent, isolated or as part of some numeric or structural chromosomal disease or monogenic disorder. They affect male and female, with a higher frequency in male. They are present from the first years of life, are progressive and could determine important respiratory and cardiovascular symptoms.

Pectus excavatum (PE) is the most common congenital sternum abnormality (90%); it affects 1 from 300-400 births, predominantly in males (male: female ratio 3:1) [1]. Usually, it is presented at birth and it becomes more pronounced in puberty. The deformity severity and the chest asymmetry varies from a mild to severe form of PE, in some cases the sternum almost touchesd the spine. It is associated with altered pulmonary function on the strength of decrease in intrathoracic volume secondary to the sunken chest [2, 3]. Several studies tried to prove this theory but the results are not clear enough [3, 4]. The malformation can determine heart function disturbances as a result of left ventricle anterior indentation. It could be part of genetic sindromes like Jeune's Syndrome, Marfan Syndrome, Noonan Syndrome.

Pectus carinatum (PC) is an abnormal protrusion of the anterior chest wall. It appears in 5-6% of cases of congenital sternum malformations, male: female ratio 4:1 [5]. It affects 0.06% of the population and about 25% of them have positive family history of sternal abnormalities [6]. There are two types of PC, chondrogladiolar or chondromanubrial, according to the prominence site. Studies showed a higher incidence of cardiac and hemodynamic changes in chondromanubrial abnormalities [7]. PC is associated with respiratory symptoms like dyspnea or tachypnea because of fixed antero-posterior diameter of chest wall that became rigid [8]. However, 22% of patients from one series were asymptomatic [6]. Another significant problem of the malformation is the concern about the body image associated with low self-esteem [9]. Like PE, PC may occur in association with other clinical symptoms as part of genetic syndromes—Trisomy 18, Trisomy 21, Marfan syndrome, Osteogenesis imperfect.

The cleft sternum, a total or partial fissure in the middle of the sternum, is a very rare sternal abnormality. It appears as a result of a disturbance in the embryologic sternum development.

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Pentalogy of Cantrell is a very rare congenital malformation; it is represented by 5 major malformations: midline supraumbilical abdominal wall defect, the sternal lower part defect and agenesis of the anterior portion of the diaphragm, an absence of the diaphragmatic part of the pericardium and a malformation of cardia. It affects 1/65,000-1/200,000 live births [10]. The pathology may occur sporadically or in association with other genetic syndromes like Down syndrome, Turner Syndrome, Trisomy 13 or 18.

Asphyxiating thoracic dystrophy is named Jeune syndrome. It consists in small chest, short ribs, and shortened bones in the arms and legs; there also could appear other symptoms like polydactyly, an extremely narrow, bell-shaped chest. It is a rare skeletal pathology; it affects 1 in 100,000 to 130,000 people [11].

Spondylothoracic dysplasia, Jarcho-Levin syndrome, another rare chest wall malformation, is characterized by short and rigid neck, shortened thorax, protuberant abdomen, inguinal and umbilical hernias and moderate to severe scoliosis and kyphosis. The literature describes only 14 cases till now.

The etiology of all congenital sternum abnormalities are not clearly identified yet even if a family tendency was tried to be proved.

Objective. The study aims to highlight the genetic origin of the most common congenital sternum abnormalities (PE and PC) and the role of specific genes in the appearance of those deformities.

Material and Method. We performed a literature review to identify the most relevant studies for our topic. We reviewed data bases like PubMed, Orphanet and The Cochrane Library and online archives of journals like The Lancet, European Journal of Human Genetics, Genetics in Medicine, Human Genetics. The search strategy was based on key words like “gene”, “genetic factors”, “sternum abnormalities”, “congenital sternal malformations”, “pectus excavatum” and “pectus carinatum” used alone and in combination (table 1). We included all published studies that corresponded to our research strategy, with no study design restrictions. We did not filter the studies according to the participants or the published year. Our review targeted infants, children or adults with PC or PE. We excluded studies who present the management, the treatment or any other different information by the genetic part of the targeted pathology. We also excluded the studies that presented syndromic PE patients. The titles and abstracts of studies that were detected by our research strategy were evaluated by all the authors independently for inclusion all the potential studies in our review. For eligible studies, at least one review author extracted the data using the agreed form. We resolved disagreements through discussion between all the authors.

Results. We detected 402 possible eligible studies and after the evaluation according to the inclusion criteria 392 were excluded. Excluded causes were presented in methods section. From the included studies, 8 studies present genes involved in PE appearance, 1 study for PC appearance and 1 study for pectus deformity (PE and PC).

Song Wu et al. analyzed a four-generation Chinese family with congenital PE [12]. DNA samples from the tested persons were whole genome sequenced for four affected members of the family and also for one unaffected. They identified a mutation on chromosome 7, g.chr7: 99764688G>A, in affecting members of the family. The mutation affects the first exon of GAL3ST4 causing a substitution of arginine with tryptophan. The mutation did not appear in healthy tested persons. The first results indicated a specific mutation for PE, but in order to validate them, the research team genotyped a cohort of 378 unrelated healthy individuals and they observed none of the normal tested person had it. They also sequenced the whole exon of GAL3ST4 in another eight individuals with sporadic PE and identified the mutation g.chr7: 99758263C>T in one person [12].

As part of the clinical symptoms in Marfan syndrome, PE was evaluated in a study published by Eliana Disabella and Co in 2005. They identified two new mutations of the TGFBR2 gene in patients non-carriers of FBN1 gene defects. Those patients had major cardio-skeletal signs and no major ocular abnormalities. One of them, a 27 years old male, had an extremely pectus excavatum associated with other skeletal malformations. This case had M425V mutation of TGFBR2; the mutation was absent in healthy tested people. The case of a 4 years old girl had pectus carinatum and she was detected to carry a novo D446N mutation. Another presented case with severe cardio-skeletal malformations associated pectus excavatum with R460H mutation [13]. The authors concluded that the three identified mutations are located in the serine/threonine kinase domain of the TGFBR2 which affecting serine/threonine kinase domains involve signal signaling and transduction mechanisms determining connective tissue disorders and cancer [13].

We identified a study from 2004 by Ghazala Mirza et al. that described two patients with mild PE associated with deletion of BMP6 gene located on chromosome 6[14]. Similar studies on mice revealed sternum malformations associated with the same gene mutation which allowed the authors to suggest that the specific protein has a similar role in humans and mice [15].

A mild form of PC was reported by Ofner et al. as part of clinical manifestations of deletion on paternal chromosome 5, 5q21.1-23.1. The deleted region contains several genes involved in the tissues and bone development [16].

Komatsuzaki et al. analyzed the mutations on SHOC2 gene in patients with Noonan-like syndrome. They analyzed 92 patients and tried to compare the frequency of clinical symptoms between patients with SHOC2 gene mutation associated with Noonan-like syndrome and patients with Noonan syndrome, Costello syndrome and cardio-facio-cutaneous syndrome. They concluded that pectus deformity was 72% more frequent in SHOC2 mutation [17].

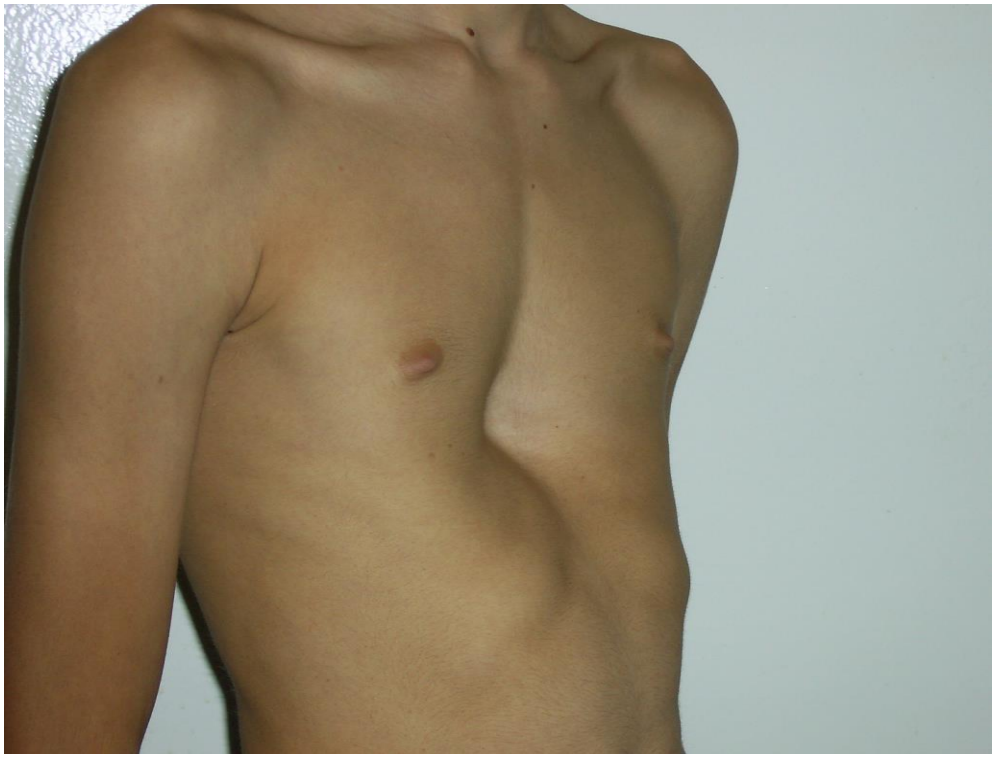

Fig. 1. Pectus excavatum.

#63	Add	Search (((("sternum") AND "pectus carinatum")) AND "genetic factors"	0	06:07:26
#62	Add	Search (((("sternum") AND "pectus excavatum")) AND "genetic factors"	0	06:06:57
#61	Add	Search (((("sternum") AND "pectus carinatum")) AND "gene"	0	06:06:26
#60	Add	Search (((("sternum") AND "pectus excavatum")) AND "gene"	1	06:05:28
#24	Add	Search ("genetic factors") AND "pectus carinatum"	1	06:02:57
#25	Add	Search ("genetic factors") AND "pectus excavatum"	1	05:56:37
#28	Add	Search ("congenital sternal abnormalities") AND "gene"	15	05:27:16
#29	Add	Search ("congenital sternal abnormalities") AND "pectus excavatum"	74	05:20:39
#30	Add	Search ("congenital sternal abnormalities") AND "pectus carinatum"	32	05:08:18
#27	Add	Search "congenital sternal abnormalities"	882	03:25:51
#23	Add	Search "genetic factors"	25044	03:03:27
#22	Add	Search ("sternum") AND "pectus excavatum"	368	02:58:35
#21	Add	Search ("sternum") AND "pectus carinatum"	123	02:58:20
#20	Add	Search ("sternum") AND "gene"	142	02:57:42
#19	Add	Search "sternum"	10763	02:57:25
#18	Add	Search (((bone) AND "chest wall")) AND "gene"	13	02:56:59
#17	Add	Search ("breastbone") AND "gene"	1	02:56:29
#16	Add	Search ("pectus carinatum") AND "gene"	17	02:56:07
#15	Add	Search ("gene") AND "pectus excavatum"	37	02:55:53
#14	Add	Search "gene"	1637992	02:55:46
#13	Add	Search (((bone) AND "chest wall")) AND "pectus excavatum"	117	02:55:31
#12	Add	Search (((bone) AND "chest wall")) AND "pectus carinatum"	53	02:55:20
#11	Add	Search (bone) AND "chest wall"	3241	02:54:58
#10	Add	Search bone	1025454	02:54:51
#9	Add	Search "chest bone"	15	02:54:28
#8	Add	Search "chest wall"	13440	02:54:09
#3	Add	Search "pectus carinatum"	293	02:51:13
#2	Add	Search "breastbone"	25	02:50:57
#1	Add	Search "pectus excavatum"	1514	02:50:46

Table 1. Search strategy on PubMed.

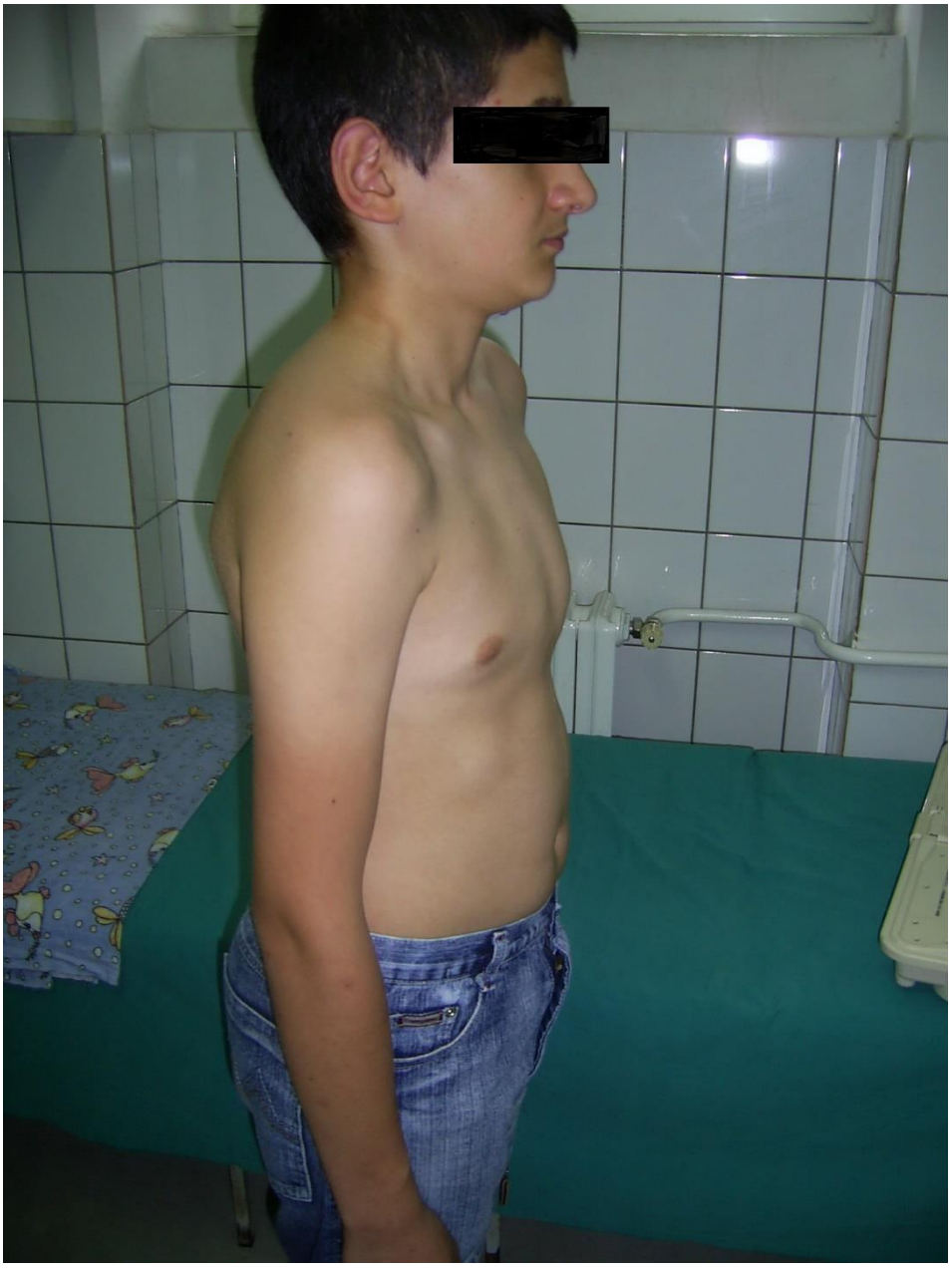

Fig.2. Pectus carinatum.

Gurnette et al tried to map the genes causes adolescent idiopathic scoliosis (AIS) and PE. They evaluated a 5-generation Caucasian family in which segregate. They performed a genome-wide linkage analysis for thirteen affected members of the family, nine female affected by AIS, 3 male and one female affected by PE, and also for ten unaffected members of the same family. The analysis revealed a novel locus for PE and AIS on chromosome 18, 18q12.1–q12.2. In the end, the authors tried to highlight that the genetic conditions of those two bone malformations are likely related [18].

FBN1 gene mutations, the genetic cause of MSS (Mitral valve prolapse, not progressive Aortic enlargement, Skeletal and Skin alterations) is also commonly associated with PE [19].

Several studies tried to demonstrate the genetic condition of PE analyzing the pedigree of families with more than one affected individual. In one study, the authors revealed four families with an autosomal recessive inheritance, six families X-linked recessive inheritance and fourteen autosomal dominant inheritance of the medical condition [20]. Lisa Horth and Co evaluated 48 pedigrees and 56 clinical traits and obtained important evidence of the genetic control of the disorder [21]. They also demonstrated the higher prevalence of PE in male.

Stacey and Co supposed that costal cartilage of patients with PE has modifications of variable number of tandem repeats (VNTRs) of ACAN gene that compromised structural characteristics. They identified an increase

severity of PE in female associated with a decreased number of VNTRs which weakened the cartilages [22].

Discussions. Only 10 studies were eligible to be included in our review. Two studies tried to highlight the inheritance character of PE evaluating the pedigree of families with more than one affected individual. Even if those studies did not present any specific gene for congenital sternal abnormalities, we included them in the review because their outcome was similar with what we needed. Another two studies evaluated the genetic cause of PE or PC like part of two genetic syndromes. We also included them because they presented Marfan and Noonan syndrome determined by new genes which could be associated with severe malformations of sternum.

Conclusions. All the described studies sustain the genetic origin of PE and PC. It has large limits that make almost impossible in this moment to estimate a precise contribution of genetic factors in congenital sternum abnormalities : chromosome 5 or chromosome 18 abnormalities, different gene that can also be the cause of undiagnosed disorders, known syndromes but with a different nonspecific genetic profile. The evaluation of pedigree in families with more than one affected individual is recommended like first step to identify a family predisposition for PE. The genome-wide linkage scan is the most used analysis that can determine gene mutations for PE. We need more studies with large cohorts to prove the prevalence of genetic factors in PE. It is very important to have indicators that predict a high risk of PE appearance because of its cardiovascular and respiratory complications, with a vital impact.

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EPIDEMIOLOGY OF PEDIATRIC BURN INJURIES TREATED IN THE DEPARTAMENT OF PEDIATRIC SURGERY TARGU MURES BETWEEN 1ST JANUARY 2007 AND 31ST DECEMBER 2011. A RETROSPECTIVE STUDY

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Abstract

The burn is depicted as a traumatic lesion provoked by several possible agents (thermal, chemical, mechanical, or electrical) involving different skin layers to a certain degree. Children are considered a risk group because most of them cannot protect themselves. We included in our study 411 pacients presented in the Departament of Pediatric Surgery of the Emergency County Hospital Mures between 1st of January 2007 and 31st of December 2011, diagnosed with burn injury. A total of 112 (27,25%) needed hospitalization. Analysing the distribution of the patology by sex, the data emphasize a proportion of 55,23% in the male population. A proportion of 71,42% provided from rural areas. . The most common lesion mechanism was scald, with 52,34% of total cases, followed by flame injuries with 27,09%. From topographic point of view, most of the burns were located to the upper limbs, 205 (49,87%). The average of hospitalization days was 13,11. We requested help from other specialities for 8 patients.

Most of these wounds can be ambulatory treated. Patients under 6 years are dominated by scalding burns that dropps with age, while the flame burns have a reverse trend. Most burns were found in the upper limbs, which proves that the lesional mechanism was determined by the child's desire to explore, rather than because of the accident. We believe it is important to establish serious prevention initiatives for these injuries. Even though they play an essential role in children trauma, burns have low mortality and morbidity rates.

Key words: burns, epidemiology, children

Backround

The burn is depicted as a traumatic lesion provoked by several possible agents (thermal, chemical, mechanical, or electrical) involving different skin layers to a certain degree.

Children at greatest risk are those who cannot protect themselves. Children with neurologic disorders, disabilities, and developmental delays also present a higher risk from inability to protect themselves and have a higher incidence of preventable injuries, have extended hospitalizations, and bear significantly higher mortality risks.(1) Children may sustain burn injury through a variety of different energy sources which include thermal, electrical or chemical. Burns account for the greatest length of stay of all pediatric hospital admissions for injuries (2) and costs are substantial, with many hours of wound care and follow-up visits necessary, sometimes lasting months to years (3).

Assessment of the clinical situation is based on (1) evaluation of the total body surface of the burns, and (2) estimation of burn depth. Burn severity is dictated by: (a)percent total body surface area (TBSA) involvement, (b) depth of burn injury (table 1), (c) age, (d) smoke inhalation injury, (e) associated injuries, (f) delay in resuscitation. From TBSA point of view, in children we use an estimating system called Lung-Bowder diagram for extent of burns, adapted from The Treatment of Burns, edition 2, Artz CP and Moncrief JA, Philadelphia, WB Saunders Company, 1969. The problem in treated different than in adults because children have proportionally larger heads (up to 20%) and smaller legs (13%) than adults.

Jackson describes three concentric zones in the burn wound, that supplies a practical basis in intendance of burn injuries. The central area of the bun wound, that having most close contact with the lesional mechanism, is called the zone of coagulation. This area is characterized by coagulation necrosis of the cells. Concentrically, from this zone, extends an area of dermal ischemia called the zone of stasis. This condition is not lethal for the cells. Peripheral, it is described a zone of minimal injury, appointed the zone of hyperemia, which will recover after a period of 7 to 10 days. (4)

Material and methods

We included in our study all the pacients presented in the Departament of Pediatric Surgery of the Emergency County Hospital Mures between 1st of January 2007 and 31st of December 2011, diagnosed with burn injury, hospitalized or ambulatory treated.

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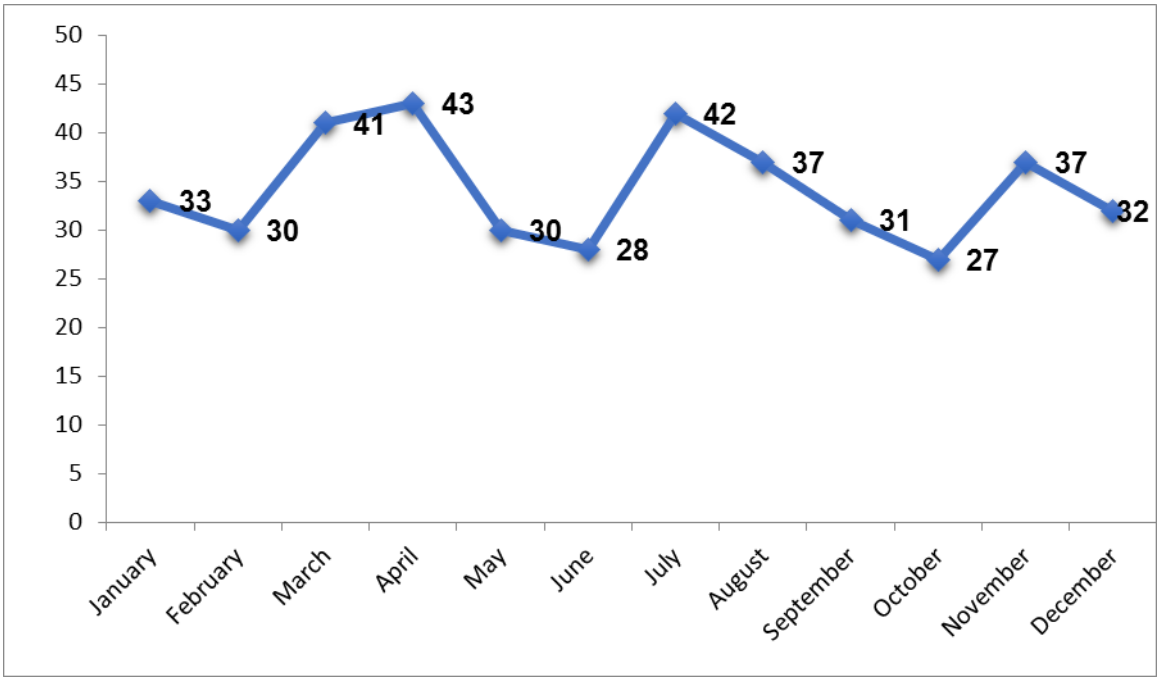

Fig. 1. Distribution of burn injuries during the year.

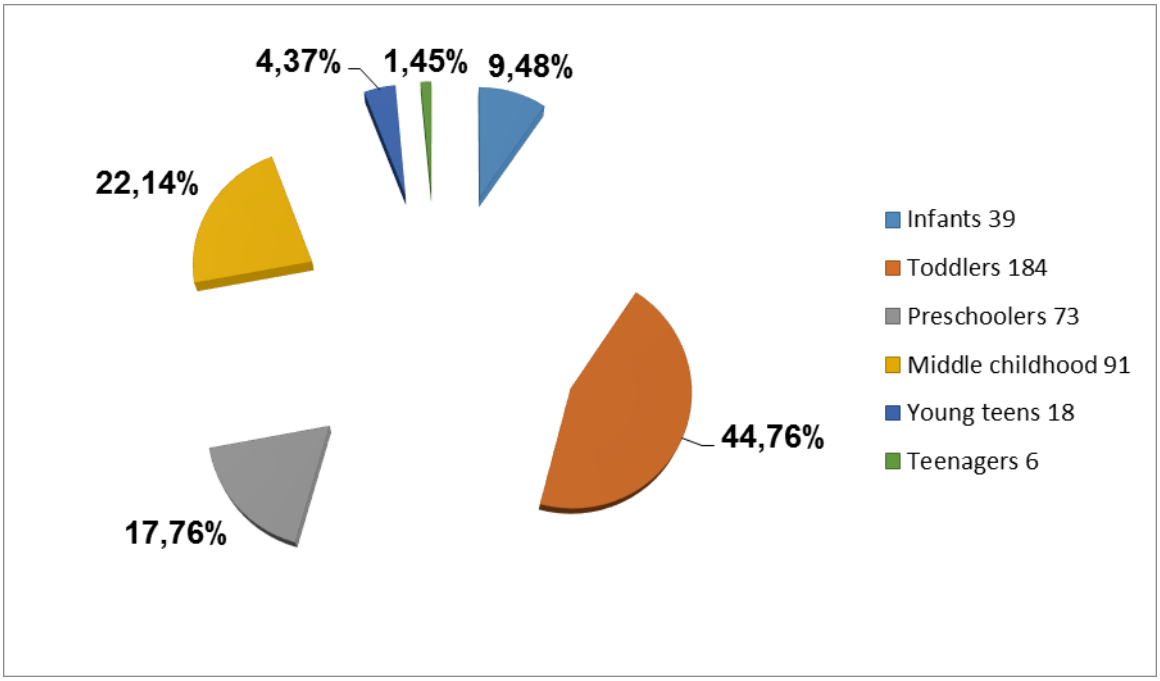

Fig. 2. Distribution of cases on groups of age.

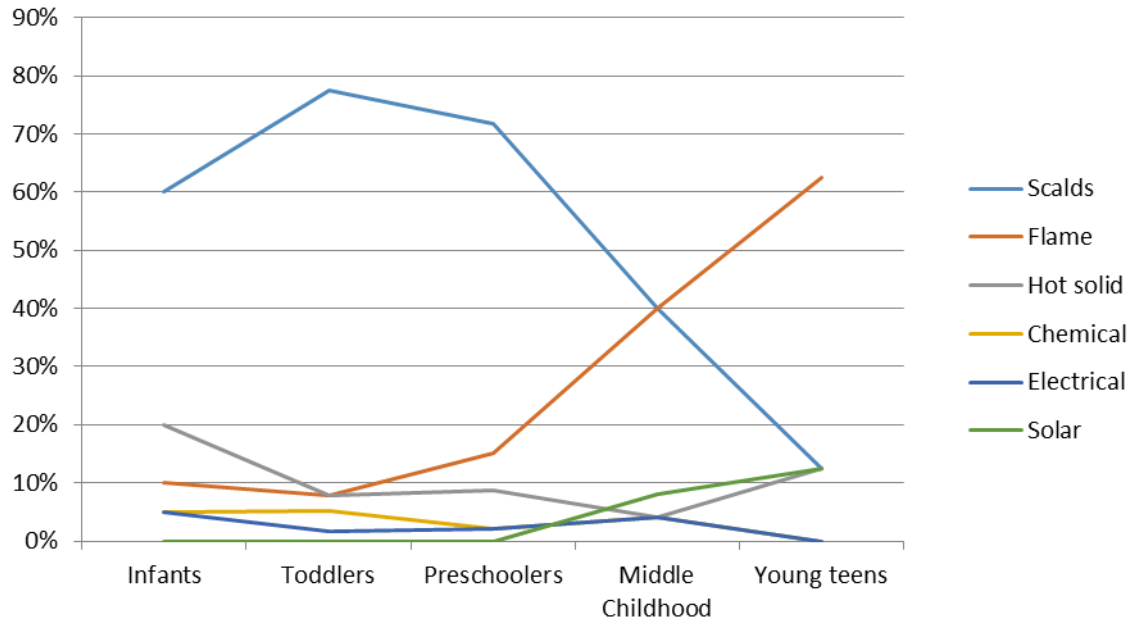

Fig. 3. Epidemiology of burns.

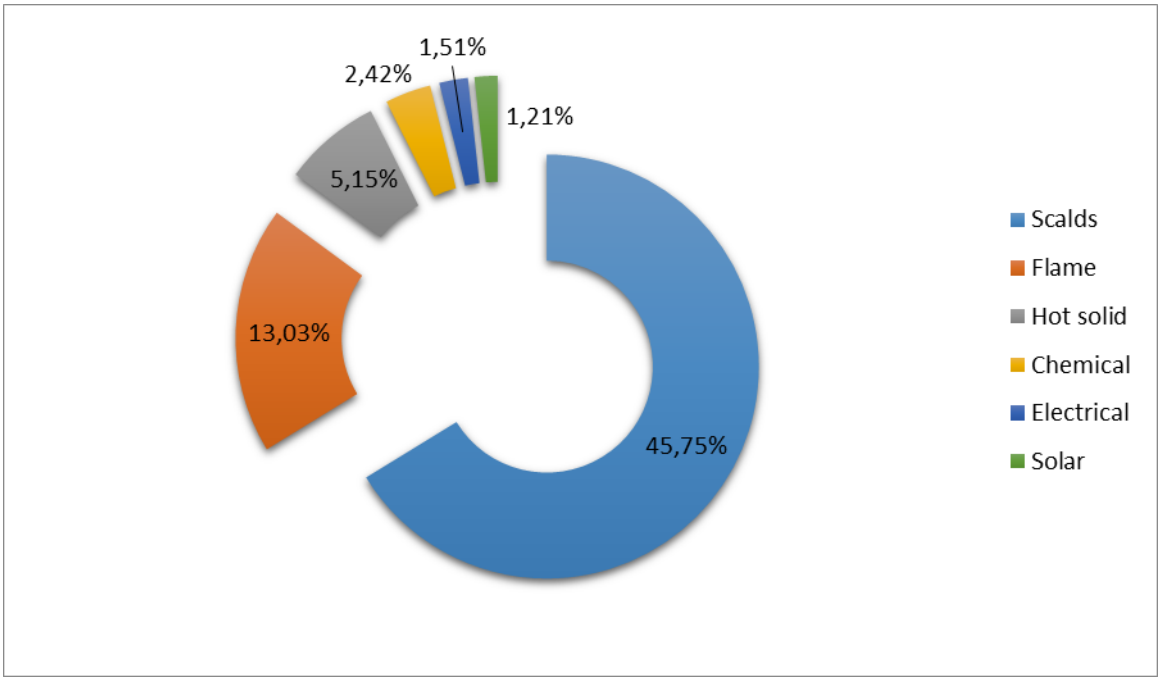

Fig. 4. Etiology of burns.

We used American Burn Association criteria for admission in the hospital, as follows: (1) partial-thickness burns of greater than 10% of the total body surface area, (2) burns that involve the face, hands, feet, genitalia, perineum, or major joints, (3) third-degree burns in any age group, (4) electrical burns, including lightning injury , chemical burns, (5) burn injury in patients with preexisting medical disorders that could complicate management, (7) any patients with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality, (7) burned children in hospitals without qualified personnel or equipment, (8) burn injury in patients who will require special social, emotional, or rehabilitative intervention.

As the child's respiratory and cardiovascular status was stabilized, attention was directed toward the management of the burn wounds. Immediately following injury, clothing was removed, and a total survey of the body was performed in a clean, warm environment. In children with large bums, assessing only a portion of the body at a time was necessary to maintain the child's temperature. Less obvious areas of injury, such as the scalp and oropharynx, were examined for evidence of thermal injury. Regular assessment of peripheral pulses was performed on involved extremities. Surgical escharotomies was required during the resuscitation phase in some cases to restore effective circulation to extremities and digits. After the escharotomy has been performed, the neurologic status of the affected limb was assessed frequently because peak edema fonnation does not occur until 24 hours after the bum. Wounds were cleaned with antibacterial substances and sterile water or NaCl. Loose tissue was mechanically debrided, and the prescribed topical agent was applied. The head and extremities were elevated for comfort and to minimize fluid accumulation.

Results

We registered a 411 cases of burn injuries, of which a total of 112 (27,25%) needed hospitalization,the rest being ambulatory treated . The distribution of cases during the year was uniform, with a peak in April, when 43 cases were registrated (figure 1). Most cases were recorded in 2010 (92 representing 22,38%), the least being in 2008 (67 representing 16,30%).

We divided patients by age, related to CDC (Centers of Disease Control and Prevention) in 6 groups: I-infants(0-<1 years of age), II-toddlers(>/=1-<3 years of age), III-preschoolers(>/=3-<6 years of age), IV-middle childhood(>/=6-<12 years of age), IV-young teens(>/=12-<15 years of age), V-teenagers(>/=15-<18 years of age). Most cases were found in the toddlers group (114 means 27,73%), highlighted in figure 2.

Analysing the distribution of the patology by sex, the data emphasize a proportion of 55,23% in the male population. 71,42% of our study patients are from rural areas. Table 1 lists the burning agents by age group. It is easily remarkable that scald injuries occurs in infants and toddlers goup, but they progressively decrease with age (figure 3), while flame injuries had a reverse shape. There were to few cases in teenagers group to be turned into percentage. The most common lesion mechanism was scald, with 52,34% of total cases, followed by flame injuries with 27,09%.

From topographic point of view, most of the burns were located to the upper limbs, 205 (49,87%), the rarest being registrated int the external genitalia region. The other body segments were affected like this: head and neck 95 (23,11%), trunk 118 (28,71%) and inferior limbs 152 (36,98%).

A number of 376 patients (91,48%) presented 2nd degree burns, 115 (27,98%) 3rd degree, 107 (26,03%) 1st degree and only 9 (2,19%) has 4th degree burns.

Using Lung-Bowder diagram for extent of burns, we had 322 (78,35%) burns <10% body surface (BS), 53 (12,90%) patients with burns </=10-<10% BS, 23 (5,60%) </=20-<30 BS an 13 (3,16%) patients with burns involving up to 30% BS. We hospitalized 112 (27,25%) patients, the rest being ambulatory treated, until the wound presented signs of epithelization. Of all hospitalized patients, 4 patients were discharged on request on their own responsibility, being treated as outpatient. A number of 19 patients refused the admission, against to physician's recommendations. The average of hospitalization days was 13,11 days, with a peak of 99 days, and a minimum of 1 day. In this estimation, we did't consider the patients discharged on request. 4 of our hospitalized patients needed intensive care support, so they were transferred in the pediatric IC unit, the average of days spent here being 8. One death has been registred after 12 days of intensive care, in a 3 years old girl with grade 2,3 and 4 burns on 35% BS, after flame injury.

All of the patients who presented in our service with burn injuries received antitetanic vaccine, wound cleaning and dressing. The hospitalized patients were treated as follows: 56 (50%) needed excisional debridement, 44 (39,29%) received nonexcisional debridement, 11 patients required skin grafts, 5 (4,46%) on less than 3% BS and 7 (6,25%) on more than 3% BS. In 58 (51,79%) cases we used general anesthesia for doing the surgical maneuvers, the rest receiving proper pain management. One patient needed mechanical ventilation for vital functions support, and another one requested surgery for correcting the scar contracture; we used local skin flaps technique (z-plasty) .

We requested help from other specialities for 8 patients(1,95%), like this: 2 dermatological consults, 2 infectious diseases consults, 2 ophtalmological consults, and plastic surgeons opinion for one patient.

Discussions

Most researchers who have studied in depth the epidemiological problems of burns in children have reached the same conclusion: the most important thing in the management of burns in children is prevention. Cohen and Swift came to help in this problem by developing a framework of counter measurements for a large scale application, in Spectrum of Prevention. A first step in this initiatives has to be to recognize that adequate supervision of children remains a major prevention tool for avoiding accidents of all type. Studies demonstrated that lack of

supervision is the the first reason attributed to burns accidents.(5)

In terms of gender distribution we obtained comparable results to Orozco-Valerio's study (6), where the injuries in male population was three times higher than in female one, and also more important. There are several studies that indicate higher incidence of burns in boys. (7),(8),(9),(10),(11)

We divided our patients by age group, and we found most cases in toddlers group (>/=1-<3 years). Consistent to our data are El-Badawy's results (7), who found 57% burns in children younger than 4 years old, with a maximum under 2 years old, the same with Híjar-Medina's data (8), and Orozco-Valerio who found 48,3% burns under 2 years of age. (6) Lari (9) and Gari (11) have data in the same frame, in studies conducted in Iran, respectively Nigeria.

The main mechanism of injuries is represented by scalds, followed by flame injuries. The same classification was obtained in more other studies, with a very similar percentage. Orozco-Valerio reported 55,9% scalds and 28,0% flame injuries (6), Rawlins counted 51% scalds (12), Forjuoh obtained a percent of 58 scalds (13), and Lari's study returned 46,2% (9). As in our results, Gupta specify greater preponderance of burns in children less than 5 years, in older children flame injuries being prevalent (10). Also, many other studies certify the predominance of scald burns. (11),(14),(15). Scald injuries can be caused by any type of hot liquid including tap water, tea and coffe and more viscous liquids such as soups, grease and tar (11).

Mashreky described in two successive studies developed in Bangladesh a significant diference in terms of the number of burns in rural and urban, with a prevalence of 4 times higher in rural areas (16,17). In our results we find a dierence more than 2 times higher for the patients from rural areas.

Our patients was discharged after the rebalance of vital functions, fluid resuscitation, pain management, setting a custom nutritional formulas, burn wound management, in a condition that allows us to treat him ambulatory. The average of hospitalization days was 13,11 days, not far from Forjuoh's work, who reported an average of 13,4 days. (13)

Conclusions

Burns remain an important cause of injury in children besides efforts to improve the treatment of these patients. Most burns occur in children under 3 years, which reinforces the idea that the mechanism of these lesions recipes always related cognitive and motor functions in connection with child's ability to explore the environment, lack in assessing possible hazards, and not finally, the negligence of parents. We believe it is important to establish serious prevention initiatives for these injuries.

Most of these wounds can be ambulatory treated. Patients under 6 years are dominated by scalding burns that dropps with age, while the flame burns have a reverse trend. Most burns were found in the upper limbs, which proves that the lesional mechanism was determined by the child's desire to explore, rather than because of the accident. Also, most burns were 2nd and 3rd degree, because the children's self-defense reflex mechanisms are not well developed.

Even though they play an essential role in children trauma, burns have low mortality and morbidity rates.

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PEDIATRIC TRACHEOTOMY: INDICATIONS AND COMPLICATIONS IN THE PEDIATRIC HOSPITAL "LOUIS TURCANU"

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Abstract

Tracheotomy is a surgical procedure in which a direct airway is open in the trachea. Conventional tracheotomy is the procedure of election in pediatric patients. The goal of this study was to assess the indications and complications of pediatric tracheotomies performed in the Department of Pediatric Surgery of the Pediatric Hospital "Louis Turcanu" in Timisoara, from July 2011 to February 2013. Over the studied period 7 tracheotomies were performed. 6 (85.71%) were male and one (14.28%) was female. The age of the patients ranged between 3 months and 10.5 years, with a mean of 24.71 months. 6 of the patients (85.71%) were under one year of age. . In 5 of the 7 cases (71.42 the main indication was prolonged orotracheal intubation. In two cases (28.57%) tracheotomy was performed for upper airway obstruction. The overall rate of complications was 42.85%. They were all early complications: intraoperative bleeding in two cases and pneumothorax in one patient. Decannulation was performed successfully in 2 patients (28.57%). The overall mortality rate was 42.85% (3 patients) and was due to the primary diseases with no relation to tracheotomy. The main indication for tracheotomy in our study was prolonged intubation. The incidence of complications was acceptable, comparable with other studies in the literature. The reduced number of patients is a limitation of our study.

Key words: pediatric tracheotomy, indications, complications

Introduction

Tracheotomy is a surgical procedure in which a direct airway is open in the trachea.

Two main techniques are used today: the surgical tracheotomy and the percutaneous dilatational tracheotomy. The procedure of election in pediatric patients is conventional tracheotomy 1. It is a potential life-saving surgical intervention, but literature suggests that the risks associated with it are significantly higher in children than in adults 2.

There are four main indications for tracheotomy: long-term mechanical ventilation, weaning failure, upper airway obstruction and copious secretions 2. During the last 3-4 decades the indications for children have changed considerably. Previously represented mainly by acute inflammatory airway obstructions, such as acute epiglottitis, croup and diphtheria, they are now replaced by long term intubation and its relevant sequelae 4-7.

The goal of this study was to assess the indications and complications of pediatric tracheotomies performed in the Department of Pediatric Surgery of the Pediatric Hospital "Louis Turcanu" in Timisoara, from July 2011 to February 2013.

Material and method

We performed a retrospective study to identify the pediatric patients who underwent tracheotomy between July 2011 and February 2013. Patient charts were analyzed with respect to age, sex, primary diagnoses and indications for the procedure, the moment for the intervention, the type of anesthesia, the outer diameter (OD) of the cannula and early and late complications.

If the main indication was prolonged intubation, we considered early tracheotomy if the intervention was performed within 7 day from the intubation.

Early complications were defined was those experienced intraoperatively or within the first week following the procedure.

Tracheotomies were performed under local or general anesthesia, after receiving informed consent of the parents. The procedure started with supine positioning of the child, with a rolled-up towel placed under the shoulders. Sternal notch, hyoid bone, cricoid cartilage were identified. A vertical incision was performed between the cricoid cartilage and the sternal notch. After the debulking of the subcutaneous fat, the dissection proceeded in the midline, dividing the strap muscles and the thyroid isthmus was exposed and retracted. After the identification of the anterior tracheal wall and of the cricoid cartilage, the later was suspended with a hook and stay sutures were placed on each side of the proposed tracheal incision. The trachea was incised vertically through the second and third or third and four rings, between the stay sutures. The tracheotomy tube was inserted, the hemostasis verified and if necessary skin sutures performed. Stay sutures were taped on the chest, to be removed once with the skin sutures, one week after the surgery.

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Results

A total of 7 pediatric tracheotomies were performed in the studied time period. 6 (85.71%) were male and one (14.28%) was female. The age of the patients ranged between 3 months and 10.5 years, with a mean of 24.71 months. 6 of the patients (85.71%) were under one year of age. In 5 of the 7 cases (71.42%) the procedure was elective, the main indication being prolonged orotracheal intubation. In two cases (28.57%) emergency or semi-emergency tracheotomy was performed for upper airway obstruction (Table 1).

In the patients with prolonged intubation, early tracheotomy was performed in one of the 5 cases (20%), after 5 days of mechanical ventilation. In the rest of 4 cases, the surgery was performed after an average of 32.5 days (between 19 and 62).

In 6 of the seven patients (85.71%), the intervention was performed in general anesthesia. In one case (14.28%) local anesthesia was used, because intubation has not been possible, due to the important hypertrophy of the tonsils and the modified anatomy of the larynx by the enlargement of the cervical lymph nodes.

The tracheal incision was placed at the level of the second and third tracheal ring in the majority of the cases. In one patient, with Hodgkin lymphoma, we performed a low tracheotomy (third and fourth tracheal ring).

In 4 of the patients (57.14%) we used 5.5 mm OD cannula, in 2 patients (28.57%) 5 mm OD cannula and in one patient (14.28%) 7 mm cannula (Table 2).

The overall rate of complications was 42.85%. They were all early complications: intraoperative bleeding in two cases and pneumothorax in one patient.

Decannulation was performed successfully in 2 patients (28.57%). The overall mortality rate was 42.85% (3 patients) and was due to the primary diseases with no relation to tracheotomy.

Discussions

Tracheotomy is potentially life-saving procedure in patients with upper airway obstruction. It is also a frequently performed intervention in cases requiring prolonged intubation, due to its numerous advantages: improvement of respiratory mechanics, reduced laryngeal ulceration, improved nutrition, enhanced mobility and speech, improved patient comfort and better clearance of secretion. Disadvantages include related complications to the surgical procedure, stomal complications, and rarely trachea-innominate artery fistula and trachea-esophageal fistula formation 3.

The main indication for tracheotomy in our study was prolonged intubation, in 71.42% of cases, the result being comparable with the literature. Butnaru et al. reported that prolonged intubation was the main indication in 57% of their series 8, Mahadevan et al. in 70% 5 and Atmaca at al. in 87% 2. In the rest of the patients in our study, tracheotomy was indicated by the upper airway obstruction, due to tumor and genetic disease. These results can be explained by the introduction of the H. influenzae vaccine in the national vaccination program and also by the advancements in the intensive care units.

Conventional tracheotomy is the procedure of election for pediatric patients and most of the surgeons prefer a vertical midline incision, considered to be associated with a lower risk of stenosis, which was also our choice.

A meta-analysis published by Griffiths et al. in 2005 reported that early tracheotomy shortened the duration of mechanical ventilation and length of ICU stay 9. De Leyn et al. consider that early tracheotomy at 7 days of mechanical ventilation is appropriate for patients in whom weaning and extubation are not likely before day 14 3. Tracheotomy has also important benefits compared to prolonged intubation: greater airway security, improved patients comfort, better oral hygiene and easier nursing care. They are balanced by complications of the procedure who include bleeding, wound infection, tracheal stenosis and possibly death and stoma related complications. In our study, early tracheotomy was performed in 20% of the patients with prolonged intubation. The moment of the intervention was decided by the intensive care specialist, taking in account the option of the parents.

Table 1. Tracheotomy indications in the study group.

Type of tracheotomy	Indication	Patients
Elective	Prolonged intubation: -neurological -muscular -infection associated to pulmonary malformation	5 (71.42%) 1 3 1
Emergency/semi-emergency	Upper airway obstruction: -Pierre-Robin sequence -Hodgkin lymphoma	2 (28.57%) 1 1
Total		7 (100%)

It is considered that paediatric tracheotomy is associated with a higher rate of complications. In our study, the overall rate of complications was 42.85%. Intraoperative bleeding was the most common complication and occurred in 2 cases. It was managed by ligation of the vessels. Pneumothorax occurred in one case (14.28%), an emergency tracheotomy in a patient with Hodgkin lymphoma, important cervical adenopathy and hypertrophy of the tonsils, which altered the local anatomy and made intubation impossible. Inter coastal drainage was done and the pneumothorax subsided. The rate of complications was comparable with literature. Ravi Kumar et al. reported a complication rate of 59% for conventional tracheotomy in adult patients 1, while Atmaca et al. reported a 29.6% complication rate in pediatric patients 2.

Decannulation was performed in 2 cases (28.56%). The low decannulation rate was associated with the high proportion of patients in the prolonged intubation group and the short follow-up period. It was carried out by replacement with a fenestrated tube and using progressively smaller tubes before decannulation. If the patient tolerated the trial without evidence of airway obstruction or respiratory difficulty, the tube was finally removed.

Failure of decannulation can occur. It is reported to range from 2-5%10. To exclude local causes, Law et al. recommended that all decannulation candidates undergo anatomic examination of the airway11.

Table 2. The OD of the cannula according to the age of the patients.

Age (months)	OD (mm)
12	5.5
7	5.5
5	5
9	5.5
3	5
11	5.5
126	6

Conclusions

The main indication for tracheotomy in our study was prolonged intubation. The incidence of complications was acceptable, comparable with other studies in the literature. The reduced number of patients is a limitation of our study.

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CLINICAL SCORES IN VIRAL DIARRHEA - LIMITS AND PERSPECTIVES

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Abstract

Although there are few studies referring to clinical symptoms in viral diarrhea (Gimenez et al 2008, Lorrot et al 2011, Zhang et al 2011), in terms of the development of predictive scores of viral etiology, the works are missing.

In the specialty works there are only 2 scores for establishing the gravity of the viral diarrhea – the modified Vesikari score and the Clark score, both of them failing to be used in the prediction of viral etiology of diarrhea (Givon-Lavy et al 2008, Freedman et al 2010, Stojkovska et al 2013).

Drafting a score of early detection of the viral etiology of acute diarrhea in children would fill a niche in the research of this disease, located on the border of interest of multiple specialties – pediatrics, laboratory medicine, family medicine, infectious diseases and gastroenterology, with the possibility of a rapid diagnostic approach and an appropriate therapeutic stance.

Key words: viral diarrhea, child, clinical scores

Introduction

Viral diarrhea is a common cause of morbidity regarding children. It is produced mainly by Rotavirus and Norovirus.

Unfortunately, in Romania the confirmation of viral etiology has not been introduced in the routine practice, that's why many children with diarrhea are being over-diagnosed with bacterial diarrhea, being treated unnecessarily with antibiotics.

The incidence of viral diarrhea is not known in Romania. Current studies show restricted groups for small geographical areas- Bucuresti -Ulmeanu 2009 (15), Lesanu 2013 (10), Cisnadie -Sârbu 2009 (13). Most studies relate to Rotavirus; Norovirus studies have not been reported in Romania. Although there are some studies regarding clinical predictors in viral diarrhea -Gimenez et al 2008 (7), Lorrot et al 2011 (11), Zhang et al 2011(19),as far as the development of viral etiology prediction scores are concerned, the specialty works are missing.

Concerning the bacterial diarrhea, the situation is happier. Since the 1980s the literature is replete with articles whose objectives include the discovery of clinical-laboratory association with high sensitivity and specificity for bacterial infection in acute diarrhea.

Velasco Cerrudo (16) tries in 1992 a score of practical use:

- Score 13-17 – high prediction (posibile bacterial);
- Score 9-12 – moderate prediction;
- Score < 12 – low prediction (unlikely bacterial).

Fontana score for predicting the bacterial etiology in acute diarrhea in childhood (5).

Parameter	Score	
	(+)	(-)
Fever> 38,5˚C	**3**	**1**
Vomiting	**2**	**3**
Blood in stool	**4**	**1**
Mucus in stool	**7**	**2**

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Velasco Cerrudo score (16)

Parameter	Score	
	(+)	(-)
Fever>38^0 C	**8**	**0**
Mucus	**8**	**0**
Blood in stool	**8**	**0**
PMN in stool	**7**	**0**

It is considerd that a score over 20 points is predictive for bacterial etiology. This score is similar to the score imagined by Fontana (3 common variables: fever, mucus, blood) but in association with the obligatory coprocitograma, a factor which Fontana added later in his study in order to correct the result.

Since 1996, the researchers' main concern is to introduce the biological tests in order to improve the sensitivity and specificity of predictive factors for bacterial etiology.

In 1996 Borgnolo (1) introduce C-reactive protein as a useful parameter in the positive diagnosis of acute bacterial diarrhea and Huicho (9) addresses in 1997 the role of fecal lactoferin.

Since 2005, in the American literature one can find two interesting articles on this topic: Denno(4) found out the association of abdominal pain, stools >5/day, fecal blood, fecal polymorphonuclears and Vernacchio(18) detected in 2006 on a sample of 604 children only two predictors (vomiting and more than 16 stools/ day).

What is the situation with viral predictors of acute diarrhea for children?

Rodrigues Cervilla 1996 (12) highlights the positive predictive factors for viral diarrhea: fever, vomiting, intravenous rehydration, respiratory signs, cold season.

There are only two scores in the literature for determining the severity of viral diarrhea: the modified Vesikari score (Vesikari 1990)(17) and the Clark score (Clark 1988) (2,3), but they can not be used in predicting viral etiology of diarrhea -Givon-Lavy et al 2008 (6), Freedman et al (8), 2010, Stojkovska et al 2013 (14).

Clark score 1988 (2,3):
Maximum score 24 points
2-8 – mild forms
9-16 – media forms
17-24 – severe forms

Clark score 1988 (2,3)

Parameter	1	2	3
Diarrhea Stools/day	**2-4**	**5-7**	**Over 7**
Duration of diarrhea	**1-4**	**5-7**	**Over 7**
Vomiting/day	**1-3**	**4-6**	**Over 6**
Duration of vomiting 1-4	**2**	**3-5**	**Over 5**
Rectal temperature	**38-38,2**	**38,3-38,7**	**Over 38,8**
Duration of temperature	**1-2**	**3-4**	**Over 5**
Behavioral changes	**Irritable//does not play anymore**	**Lethargic**	**Seizures**
Length changes(days)	**1-2**	**3-4**	**Over 5**

Vesikari Score(17)

Parameter	1	2	3
Diarrhea Number of stools/ day	1-3	4-5	≥6
Duration of diarrhea	1-4	5	≥6
Vomiting- number/day	1-2	3-4	≥5
Duration of vomiting	1	2	≥3
Rectal temperature	37,1-38,4	38,5-38,9	Over 39
Dehydration	without	1-5%	Over 6%
Treatment	Rehydration	Hospitalization	

Maximum score 20
<7 mild forms
7-10 medium forms
≥11-20 severe forms
*Table adapted from rotavirus clinical trials using the Vesikari clinical severity scoring system (Ruuska&Vesikari, 1990).

Givon-Levi (8) compares the 2 scores in 2008, and there are considerable differences in identifying severe forms of viral-acute diarrhea in children:Vesikari score is more sensible and specific for this forms. Stojkovska and contributors (14) in 2013 confirm the same thing about Vesikari score versus Clark score.

Then why are they useful? Are they relevant in family medicine practice? Yes, they are useful, not for prospective study, but retrospective, for quantification efficiency in antiRotavirus vaccine.

After introducing bovine antiRotavirus vaccine, in 1986 (18), Vesikari noticed a decrease, not necessarily of incidence, but of severe forms, respectively lethal forms of Rotaviruses.

Also, this score is retrospectively useful for tracing the etiology because Lorrot 2011 (11), in a study of 2 years in France, observed that Vesikari score may be used in another type of diarrhea, the one with Norovirus, but in general the score is higher in forms with Rotavirus.

The development of precocious screening score of viral etiology in acute diarrhea at child will fill up a niche of searching this pathology, which concerned many specialties - Pediatrics, Family Medicine, Laboratory Medicine, Infectious Disease and Gastroenterology.

To remember in medical practice

The onset with high fever, tenesmus or abdominal pain and diarrheal stools with pathological elements with mucus, pus and blood, orientate to a bacterial etiology.The chronology of bacterial diarrhea includes general modified condition, fever, pain, diarrheal stools initial aqueous, after that with pathological elements and optional vomiting. Hydration condition is good in general or at the limit, but the aspect is dominated by septic condition.

The onset with moderate fever, frequent vomiting which are followed by diarrhea, abdominal pain and aqueous diarrheal stools orientates to a viral etiology. Clinical aspect is dominated by acute dehydration. The chronology of viral diarrhea is vomiting, moderate fever, then abdominal pain and diarrheal stools with fast dehydration.

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PERIVENTRICULAR LEUKOMALACIA – DIAGNOSIS AND MORPHOPATHOLOGY

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Abstract

Periventricular leukomalacia (PVL) is a relatively frequent disease amongst premature newborns with severe hypoxic disorders at birth. It is the principal form of brain injury in the premature infant and the predominant pathologic finding underlying cerebral palsy. The studied contingent included a number of 12,548 preterm newborns admitted in our clinic over a period of 15 years. Our aim was to analyze the risk factors involved in the occurrence of the PVL, the neurological and clinical picture, imaging investigations and morphological findings. The risk factors found for periventricular leukomalacia were: Apgar score<7 (84.43%), the presence of meconium in the amniotic liquid, uterus-placentary lesions, long labor. In the majority of cases, 2 or more risk factors were present. The cystic formations appeared in the evolution of most cases (79.05%) in the hyperechogenic area. The persistence of the cystic formations (56.09%) and/or the presence of the echographical signs of the cerebral atrophy (32%) were correlated with the appearance of the neurological disorders.

Key words: neurological disorders, periventricular leukomalacia, premature, risk factors

Introduction

Periventricular leukomalacia (PVL) is a distinctive form of cerebral white matter injury, an ischemic necrosis of the white periventricular substance near the external angles of the lateral ventricles [1,2]. The ending branches of the main vessels are leading to this region and, therefore, make it more predisposed to ischemic necrosis.

By microangiographic techniques it was demonstrated that infarction is localized at the border between the afferent branches of middle cerebral artery and efferent branches of choroidal artery. The primary lesion is a coagulating necrosis; after 5-7 days the necrotized tissue phagocytosis begins and is finalized after approximately 2-3 weeks, leading to a cavity.

Material and method

The study took place in the Premature and Neonatology Clinic of the "Louis Turcanu" Children Hospital Timisoara over a period of 15 years (1999-2012). The degree of symptoms' intensity, the hospitalization period, the severity of distant sequels, all depend on the intensity of the initial lesion as well as on the dimension and persistency of the cyst. The studied contingent included a number of 12,548 preterm newborns admitted in our clinic in the aforementioned period, of which 312 with severe hypoxic disorders at birth, 72 of them satisfying the selection criteria: proper history, clinical characteristics and distinctive imaging exploration results.

Results and Discussions

PVL, profound infarction of the white substance near the external angles of the lateral ventricles, was found in 72 cases (23.07%). This high prevalence in premature newborns is in accordance with the specifications of medical literature; it is known that 80-90% of cases appear in premature infants [3, 4]. Also, the localization of the lesion was distinctive, at the border between afferent and efferent branches of the cerebral arteries, 3-10 mm from the ventricular wall. The aspect of the ailment included severe hypoxia, both in prenatal, perinatal and neonatal period, constantly:

- prenatal appearance of the affection in 45 cases: materno-fetal infections, utero-placentar disorders, hyperbilirubinemia, green amniotic fluid, membrane rupture over 72 hours, Apgar score <7;
- in 37 of the cases prenatal factors were associated with other impairments that influenced the neuropatological and clinical features: sepsis, repeated crisis of apnea, bradycardia, bronchopneumonia, Patent Ductus Arteriousus, pneumothorax, ADRS by surfactant deficiency.

The premature newborns included in this lot had clinically presented an intense neurological profile, including: severe hypotonia, repeated crisis of apnea, diminished archaic reflexes – especially in lower limbs, convulsions (see Table I).

The intensity and duration of the clinical signs were higher in cases of PVL associated with periventricular or intraventricular hemorrhage (especially in severe forms). An associated ultrasound hemorrhagic lession was found in 30 cases (42.00%), 13 of them with germinal matrix localization and 17 with intraventricular localization (Fig 1).

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Table I. Clinical signs identified in the premature newborns.

Clinical signs	cases	%
hypotonia	48	70
repeated crisis of apnea	60	84
diminution/abolition of archaic reflexes	62	86
hyperexcitability	22	30
convulsions	20	28
opisthotonus	18	24

Ultrasound diagnosis of PVL was based on the characteristics and the localization of the lesion: echoic large band laterally positioned to the anterior horns of the lateral ventricles and to the trigons of the lateral ventricles. The hyper echogenicity in the anterior portion of the lateral ventricles has a typical localization on the anterior-external side.

The ultrasound examination was performed weekly and monitored the following aspects of the hyper echogenicity: intensity, dimension, localization, outline, homogeneity, the relation with the ventricular system. The echoic intensity of the lesion is important in order to appreciate the severity and the prognosis, especially in cases in which the evolution was towards cystic formations:

- 33 of cases (45.83%) were easy forms which presented periventricular echogenicity with an intensity
- lower than that of the choroid plexus and dimensions smaller than those of the lateral ventricular trigon (Fig. 2);
- 12 cases (16.7%) were moderate forms which presented periventricular echogenicity with an intensity
- similar to that of the choroid plexus and approximately equal dimensions to those of the lateral ventricular trigon (Fig. 3);
- 17 cases (23.61%) were severe forms which presented periventricular echogenicity higher than that of
- the choroid plexus and dimensions bigger than those of the lateral ventricular trigon (Fig. 4,5).

The visualized cystic formations were diagnosed on base of ultrasonography characteristics: transonic masses with homogeneous contents, homogeneous echogenicity of the contents, thick walls (intense echoic), single in 32 cases and multiple in 28 cases (Fig. 6). As time of appearance (excepting the cystic formations found on the first examination) the first cysts were observed three weeks after establishing the echogenicity.

The echogenicity evolution was: resorption – 12 cases, cystic formations – 49 cases (Fig. 7). Positioning of the cysts:

- in the anterior region (external angle of the lateral ventricles) – 40 cases
- posterior region (posterior side of the lateral ventricles) – 10 cases
- in only 9 cases cystic formations were found along the entire border of the lateral ventricles (Fig 8).

The anterior – external positioning of the lesions to the anterior horns of the lateral ventricles was confirmed by findings in the literature [5]; these areas are known to be susceptible to perfusion pressure and decreased cerebral blood pressure and, therefore, prone to the emergence of specific leukomalacia lesions.

The dimensions of the cystic masses are important in order to establish the prognosis and the neurological alterations over time. The cysts had diameters between 3-20mm. Increasing size of the cysts were associated with increasing risk of cerebral palsy, with a cut-off value of 10 mm and all infants with cysts larger than 20 mm in diameter had cerebral palsy. The high echogenicity (moderate and severe forms of the disease) was followed by big cysts, commonly supernumerary (29 cases – 40.27%). The severe clinical picture found in these cases included: recurrent convulsive syndrome (32 cases), severe hypotonia (12 cases), spasticity of the inferior limbs (16 cases) and opisthotonus (20 cases). Generally, the average periods of persistence were: echogenicity between 1-3 weeks and cystic formations 3 week to 3 months. In severe forms, transonic lesions and ventriculomegaly persisted until the age of 8-10 months.

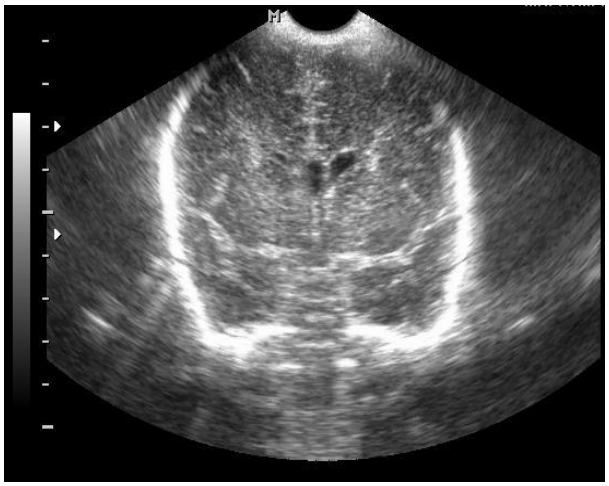

Fig. 2. LPV mild form

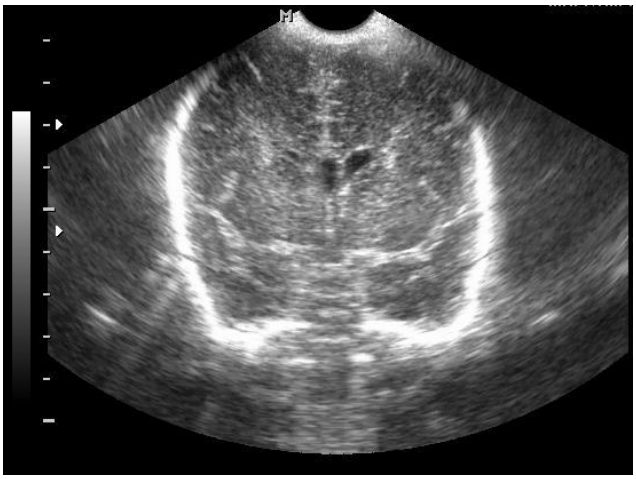

Fig. 2. LPV mild form

In the cases where the cystic masses persisted we had visualized the following aspects:
- cysts – 4 cases
- cysts accompanied by ventriculomegaly – 8 cases
- ventriculomegaly – cerebral atrophy – 23 cases

The diagnosis of cerebral atrophy was based on ventriculomegaly accompanied by the increase of the interhemispheric space and the increase of the distance between the gyrus in the anterior region.

The rupture of the septum between the cysts and the lateral ventricles produced the evolution towards ventriculomegaly. The cases in which the persistence of cystic formations was associated with cerebral atrophy, the following severe neurological modifications were found:
- recurrent convulsions – 23 cases;
- spastic dyplegia – 13 cases;
- sight disorders – 5 cases;
- speaking disorders – 4 cases;
- hearing disorders – 3 cases;
- mental retardation – 32 cases;
- minimum cerebral dysfunction – 14 cases.

The specific medical literature data referring to neurological disorders after PVL are varied. A study done by Pidcock and collabs on a lot of 127 premature newborns renders that there is a significant correlation between the appearance, dimension and localization of the cysts and the development of mental disorders. From the studied cases, 42 did not show evidence of cysts in evolution and had a good neurological outcome, unlike the 25 cases with moderate cystic lesions and the 20 cases with severe cystic lesions, which developed neurological disorders in 32% and 90% of the cases, respectively.

The association between PVL and periventricular and intraventricular hemorrhage is discussed extensively in the medical literature; most authors have observed associations in 28-59% of the cases [4,6]. In the lot that we studied there were hemorrhagic lesions (42%):
- in 13 cases subependymal hemorrhages;
- in 17 cases intraventricular hemorrhages.

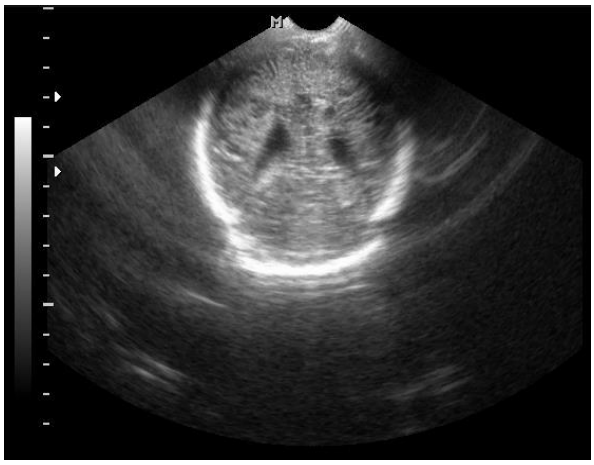

Fig. 3. LPV moderate form

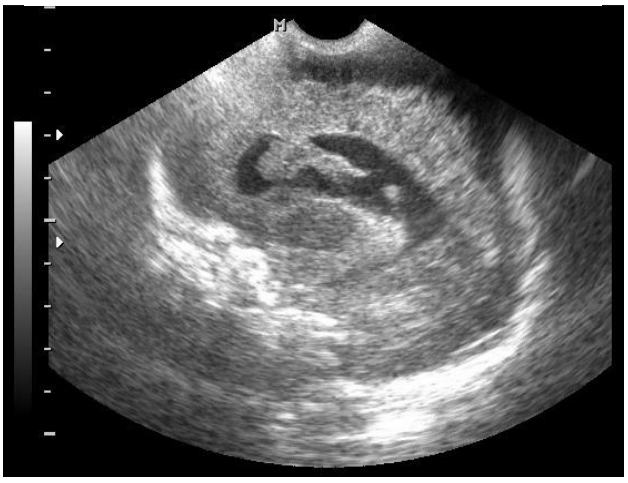

Fig. 4. LPV severe form

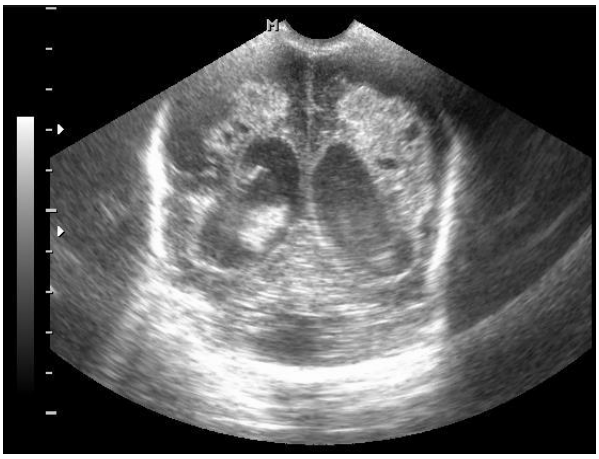

Fig. 5. LPV severe form

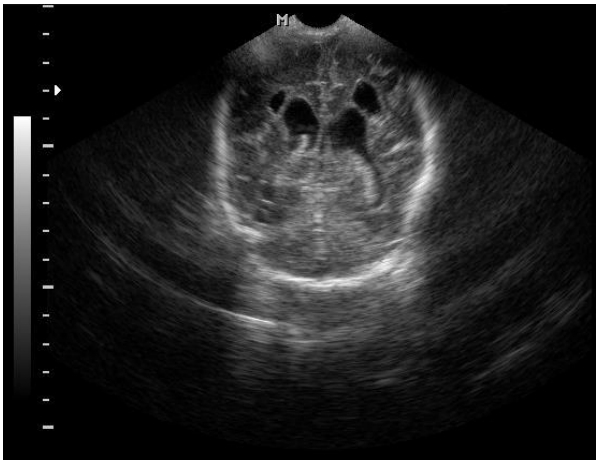

Fig 6. LPV cystic form

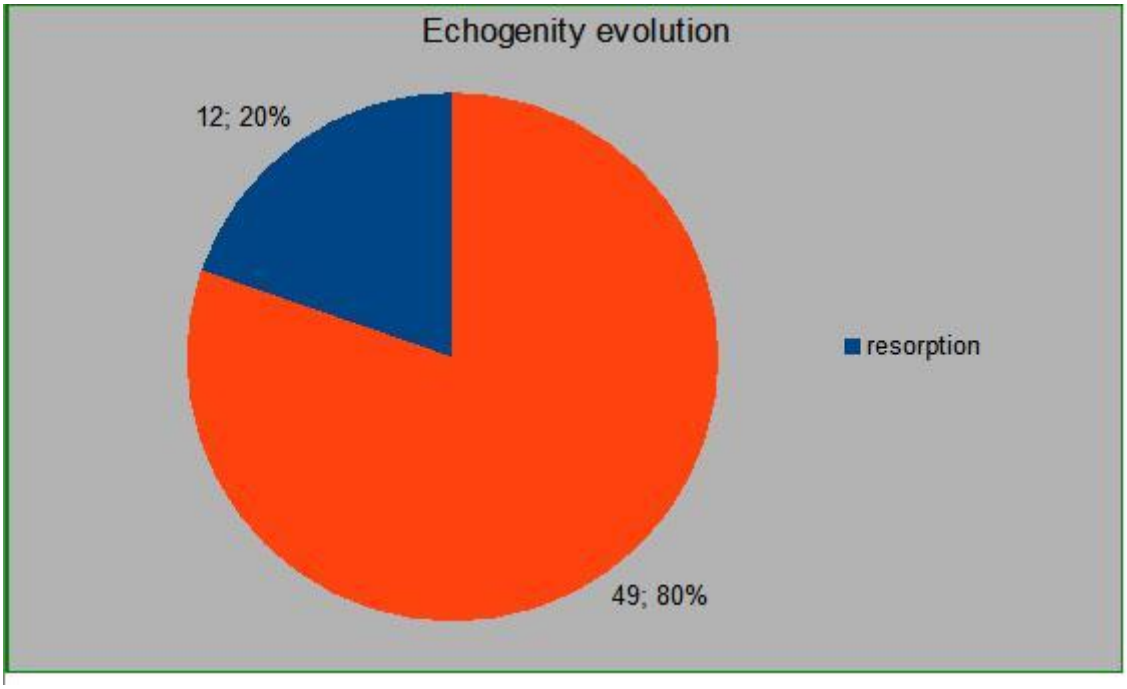

Fig. 7. Echogenicity evolution

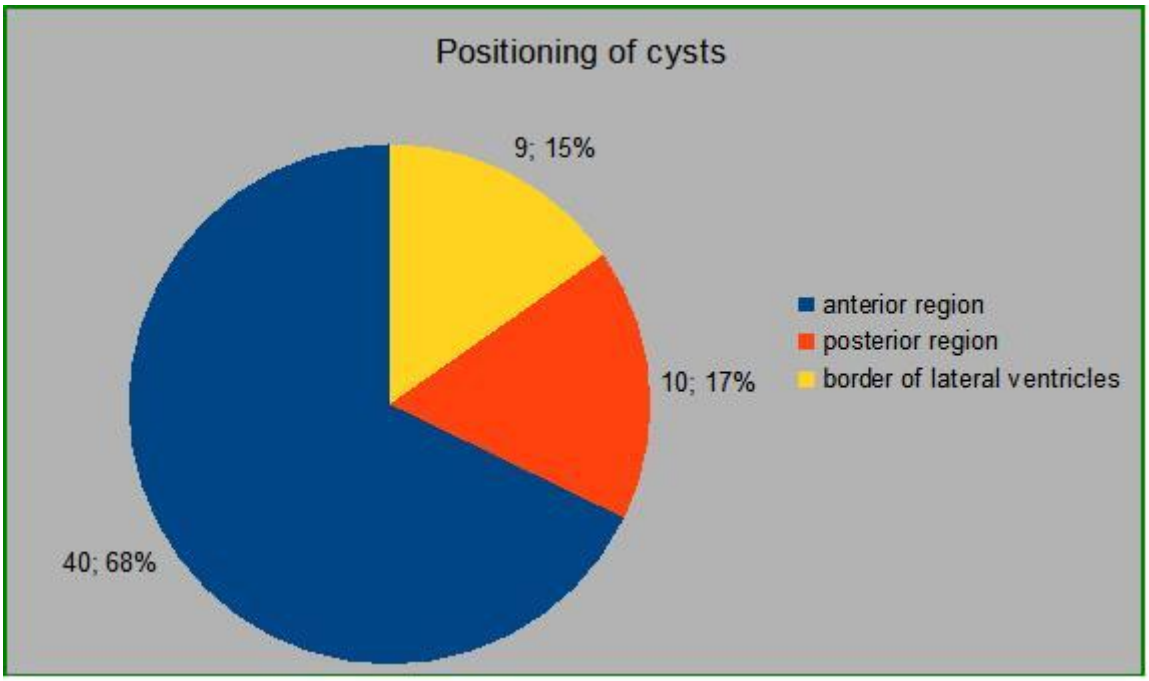

Fig. 8. Positioning of cysts

The distinction between the hemorrhagic and non-hemorrhagic PVL was difficult to prove based on ultrasonography, because the echogenicity has the same characteristics. The presence of hyperechoic lesions inside the non-dilated ventricles and in the cerebral intraventricular parenchyma (laterally from the anterior region, the posterior region and along the ventricular wall) oriented the diagnosis towards PVL associated with an intraventricular hemorrhage. In the presence of big lesions in the cerebral parenchyma, accompanied by hyperechogenicity inside the lateral, dilated ventricles, the distinction between the hemorrhagic and non-hemorrhagic forms was very difficult, as these forms represent the severe forms of intraventricular hemorrhage (IV degree).

Macroscopy:

- necrotic foci usually within 15 mm of ventricular wall, 2-6 mm in diameter, with the following common locations:
  - anterior to the frontal horn,
- lateral corners of the lateral ventricles at level of foramen of Monroe
- lateral regions of the trigon and occipital horn (including optic radiations)
- acute foci of coagulation necrosis not visible in gross;
- organized foci seen as "White spots" due to lipid-laden macrophages;
- cavitation follows, then collapse into a glial scar (or remains cystic if severe);
- long-standing damage shows thinned white matter and corpus callosum, and ventriculomegaly [7].

Histopathology:

- coagulation necrosis within 24 hours of insult (dissolution of all cell types, hypereosinophilia, nuclear pyknosis, acutely necrotic, swollen axons - spheroids - confirmed with human beta-amyloid precursor protein immunostaining;
- within a week, organization of necrosis with infiltrating macrophages and reactive astrocytes in the margin;
- in a few weeks, cavitation into periventricular cysts, collapse of cysts into glial scars with lipid-laden macrophages and mineralized axons, gliosis preferentially in deep white matter compared to intragyral white matter;
- PVL usually coexists with other perinatal pathologies including grey matter lesions;
- long-term consequence of delayed myelination (from loss of developing oligodendrocytes or from deprivation of afferent terminals from underlying white matter lesion) [7].

Joseph J Volpe [8] argued in 2009 that brain abnormality in the premature infant is unlikely to consist of a straightforward addition of destructive non-hemorrhagic and hemorrhagic lesions, such as PVL and, less commonly, GMH-IVH (germinal matrix hemorrhage/intraventricular hemorrhage) with perfusion harmonic imaging. Recent insights into the full spectrum of the encephalopathy of prematurity and into the remarkable series of developmental events that occur in the brain during this period indicate a complex amalgam of destructive and developmental mechanisms. Although further clarification of this amalgam is needed, the general principle that in the premature period brain abnormality involves destructive and developmental mechanisms seems established.

Saraid S. Billiards [9] conducted a study in 2008 on myelin abnormalities without oligodendrocyte loss in PVL, indicating that myelin abnormalities and, in some instances, loss of preoligodendrocyte lineage cell processes occur in PVL without a loss of oligodendrocyte lineage cell density. Their findings raise the intriguing possibility that a hyper acute loss of preoligodendrocyte lineages is replenished by proliferation and migration of oligodendrocyte lineage progenitors from subventricular zones, a process that may not always be adequate and thereby result in neurological disability. They also suggest that the deficits in myelination are caused by loss of oligodendrocyte lineage - cytoplasmic processes and defective myelin basic protein trafficking, perhaps secondary to process loss. The study highlights the need to analyze in greater depth the potential factors critical for oligodendrocyte lineage proliferation, migration and repair for optimal myelination in long-term survivors of PVL as crucial leads for the development of successful therapeutic strategies in PVL.

Conclusions

1. The moment of action upon the CNS was both in the ante- and intranatal period, and in the neonatal period. The risk factors were: Apgar score<7 (84.43%), the presence of meconium in the amniotic liquid, uterus-placentary lesions, long labor. In the majority of cases, 2 or more risk factors were present.

2. The cystic formations appeared in the evolution of most cases (79.05%) in the hyperechogenic area. Big cysts, usually multiple, followed the big echogenyties. In this situation, in 48.78% of the cystic formations, the clinical picture was severe.

3. The evolution towards cerebral atrophy (32%) presented the following aspects: growth of the interhemispheric space, the growth of the distance between the gyruses, the accentuated hyperechogenity of these spaces, especially in the anterior region and the slow ventriculomegaly.

4. The persistence of the cystic formations (56.09%) and/or the presence of the echographical signs of the cerebral atrophy (32%) was correlated with the appearance of the neurological disorders: convulsive recurrent syndrome (32%), infantile spastic diplegia (18%), sight disorders (8%), hearing disorders (6%) and neuro-psychomotor retardation (44%).

5. In this study we tried to present current concepts on PVL pathogenesis and underline evidence of an inflammatory pathogenic component to this illness, resulting from either hypoxic-ischemic injury or infection. These findings render the basis for clinical approaches targeted at protecting the premature brain from inflammatory alteration, which may prove beneficial for treating PVL, if identified early in pathogenesis.

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GRASS INFLORESCENCE ASPIRATION - EVOLUTIONARY FEATURES IN CHILDREN

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Abstract

The authors present the case of a child, aged 1 year and 5 months, admitted to the 2nd Pediatric Clinic of the Emergency County Hospital in Craiova, with a suspicion of aspiration or ingestion of a foreign body (grass inflorescence), which occurred during a respiratory intercurrence.

The paper describes the evolution from the first admission when the child presented poor general condition, fever, antalgic position of right lateral decubitus, abdominal meteorism, cough, respiratory failure, stetacustic lung, right axillary decreased vesicular murmur, subcrepitant rales in the right lung area. The pediatric surgery examination, the abdominal x-ray on empty stomach, and the abdominal ultrasound examination excluded the possibility of ingestion while the bronchoscopy examination revealed no foreign body. Later on, the patient presented right pneumothorax. After a calm six-month-period, the child removes, in a fit of coughing, the grass inflorescence, followed by hemoptysis. Later, bronchiectasis is highlighted, at the level of the terminal bronchus on the right side, following a bronchoscopic examination performed one month after the elimination of the grass inflorescence.

Key words: grass inflorescence, aspiration, child

Introduction

Foreign body aspiration is a medical emergency and needs special attention due to the serious effects that can lead to: acute respiratory failure, asphyxiation, heart failure, laryngeal edema, pneumothorax, hemoptysis, bronchial stenosis, recurrent pneumonia, and sometimes death (1,2).

Case presentation

Female child from urban area, aged 1 year and 5 months, is hospitalized in the 2nd Pediatric Clinic, Emergency County Hospital in Craiova, on 05/15/2012, showing fever, cough, and moaning.

Heredocollateral history: young, healthy parents; a healthy three-year-old sister; without any chronic illnesses in the family.

Physiological personal history: the second child, born after a normally developed pregnancy, born at time, in the hospital's Maternity Unit, by caesarean section, birth weight 3200g, with no birth sufferance. Breast fed for five months, fed properly with varied food from 5 months onwards, weaned at 1 year 5 months old. On admission she was eating adult food. Vaccinations were performed according to the scheme of the National Health Ministry. The prevention of rickets was performed correctly.

Pathological personal history: Frequent acute upper respiratory tract infections treated ambulatory.

Living conditions: urban housing, appropriate conditions.

Disease history: onset 5 days before admission with fever, cough, runny nose. She was investigated by the family physician who recommended treatment with Cephalexin, Nurofen, Ambroxol, Betabioptal, and Losec. The mother reported that the patient had swallowed grass inflorescence, while she had been in the yard, 2 days before admission, when she started coughing and vomiting. Later, the general condition got worse, the patient presenting again fever, spastic coughing fits, moaning; the parents presented the child for admission in the hospital.

At admission she had 38°C fever, weighed 9 kg, bad general condition, pale skin, ringed face, cyanotic color around ears and nose, dry lips, antalgic position of right lateral decubitus, spastic coughing fits, mucoserous rhinorrhea, nasal flaring, moaning, expiratory dyspnea, polypnea (35 breaths/min), intercostal and subcostal indrawing, lung stetacustic, right axillary decreased vesicular murmur, subcrepitant rales in the right lung area, rhythmic heart sounds AV= 140 beats/ min., meteorism in the abdomen, enteric transit present, normal feces.

The chest x-ray done at admission showed the emphasis of the right basal pulmonary interstitial image (Image 1).

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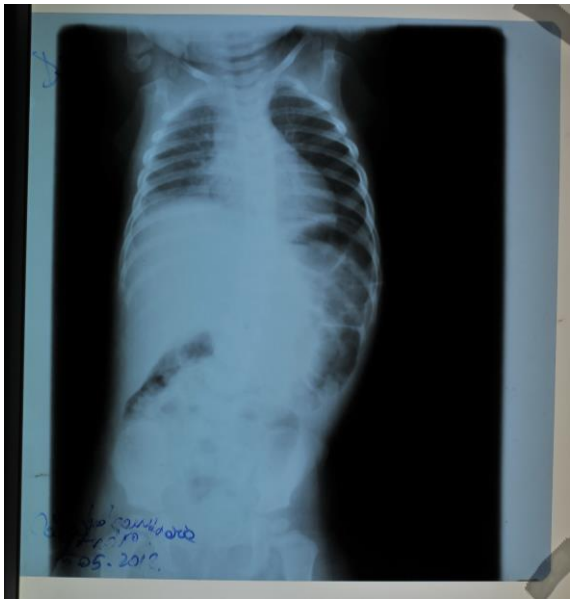

Image 1. The chest x-ray done at admission showed the emphasis of the right basal pulmonary interstitial image.

Taking into account the possibility of foreign body ingestion, we performed an urgent x-ray on empty stomach which revealed no hydro-aeric levels, a pediatric surgery examination which denied the surgical acute abdomen, while the abdominal ultrasound examination was normal. Suspecting the aspiration of a foreign body diagnosis, when admitted, the patient is sent for an Otorhinolaryngology examination, where she is recommended exploratory bronchoscopy.

Biochemical investigations: hemogram Hb= 9.6 g%, T= 452,000/mm 3, L= 40,700/mm3, NS= 72%, NN= 6%, E= 2%, M= 5%, Ly= 15%. ESR= 110/122 mm at 1/2 hours, GPT= 9 IU/l, GOT= 17 IU/l, urea= 12 mg%, creatinine= 0.44 mg%, blood ions: Na= 127 mEq/l, Cl= 98 mEq/l, K= 3.6 mEq/l, sideremy= 15µg%, calcium blood test= 2.10 mmol/L.

Emergency treatment was established: glucose and electrolytes EVP, antibiotics (Zyvoxide + Meronem), HHC, Debridat, Espumisan, rectal probe, DNF and secretion aspiration, oxygen therapy.

An emergency bronchoscopy is performed to find large mucus with pus secretion at the right primitive bronchus which is aspired; the tracheo-bronchial mucous membrane is slightly congested. Left primitive bronchus aspect is normal and does not show any pus and mucus secretions. Repeated CXR on the second day of hospitalization shows a slight ascension of the right hemidiaphragm and the reduction of the posterobasal transparency highlighting the air bronchogram, on the side incidence.

Under treatment, the general condition of the patient improved, fever disappeared, and in the second day from admission she presented productive cough, moderate expiratory dyspnea, polypnea, subcrepitant rales on the right lung area.

On the 6th day, her general condition suddenly got worse, presenting perioronasal cyanosis, groan, expiration dyspnea, lung stetacustic vesicular murmur abolished on the right lung area. Emergency chest x-ray shows total right pneumothorax (Image 2).

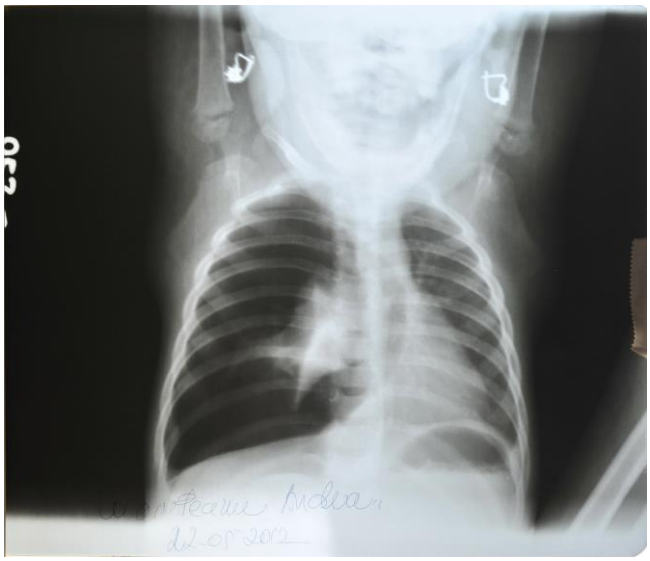

Image 2. Emergency chest x-ray shows total right pneumothorax.

The patient was transferred to the Pediatric Surgery Clinic where pleural drainage was performed and she continued the symptomatic and antibiotics treatment; the further evolution was favorable. She was discharged after 12 days of hospitalization from the Pediatric Surgery Clinic in good general condition, afebrile, rare cough, and lung stetacustic vesicular murmur present without added rales. Diagnosis at discharge: Aspiration Pneumonia. Total Right Pneumothorax. Acute Respiratory Failure. Iron Deficiency Anemia. Deficiency Rickets.

6 months after the discharge (November 2012), she showed fever, productive cough for which she received ambulatory treatment with Zinnat for 10 days. 48 hours after the treatment, fever reappeared and the parents came again with the child in our clinic and re-hospitalized her.

On admission, she was afebrile, with a fair general condition, weighed 10 kg, pale skin, the face of a suffering person, spastic cough, intercostal indrawing, stetacustic pulmonary vesicular murmur axillary decreased and in the upper right semi thorax, slender abdomen, and liver 1 cm below the costal margin. Pulmonary x-ray (on admission, 11/29/12): intense opacity occupying the right median base region, homogeneous, medium intensity, having a condensation character (Image 3).

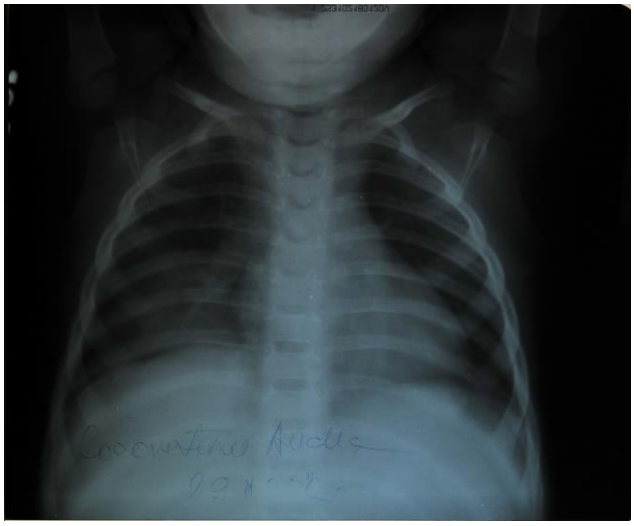

Image 3. Pulmonary x-ray (on admission, 11/29/12): intense opacity occupying the right median base region, homogeneous, medium intensity, having a condensation character.

Hemogram (BCT): Hb=10.3 g%, T= 667,000/mm^3, L= 26,600/mm^3, NN= 39%, Ly= 46%, M= 8%, ESR= 84/114 mm at 1/2 hours, fibrinogen= 260 mg%, CRP <6 mg%, urea= 27 mg%, creatinine= 0.43 mg%, glucose= 112 mg%, GPT= 12 UI/l, GOT=21 UI/l, INR= 0.92, Quick= 116%, PPTTa= 24, calcium= 1.95 mmol/l, sideremy= 41 mg%, blood electrophoretogram: Na= 136 mEq/l, Cl= 104 mEq/L, K= 3.9 mEq/l, normal urine analysis test, negative urine culture, tracheobronchial secretion culture in aerobic environments at 37^{0}C developed no pathogens.

The patient was given a treatment with Sulperazone + Zyvoxide, Dexamethasone, Salbutamol in nebulization and, Liv 52. On the second day of hospitalization she eliminated, in a fit of coughing, a vegetable residuum – grass inflorescence 2.5 cm long (Image 4); she still presented some prolonged coughing fits with fresh blood and blood clots expectoration with a hemoptysis look.

Image 4. Grass inflorescence 2.5 cm long.

Further evolution under the treatment was favorable, the patient was afebrile, she had good appetite, and coughing fits were rare. Repeated CXR highlighted positive development with marked restriction in intensity and extent of opacity mentioned above (Image 5). Repeated biochemical investigations: blood count test: Hb=10.7 g%, T= 807,000/mm^3, L= 8,400/mm^3, NS= 20%, Ly= 70%, M= 10%, ESR=23/40 mm to 1/2 hours, urea= 16 mg%, GPT= 28 UI/l, GOT= 28 UI/l, CRP <6 mg% fibrinogen= 230 mg%. She was discharged after 12 days of hospitalization with good general condition, afebrile, good appetite, no cough, lung stetacustic normal. Discharge diagnosis: Right pneumonia abscission due to foreign body aspiration (grass inflorescence). Acute respiratory failure. Hemoptysis. Iron deficiency anemia. Deficiency rickets. 1st degree dystrophy.

In January 2013 she underwent a specialized control at Marius Nasta Hospital in Bucharest where the bronchoscopy showed bronchiectasis at the level of the terminal bronchus in the right lung area.

Further evolution was favorable. The patient appears in our clinic's records.

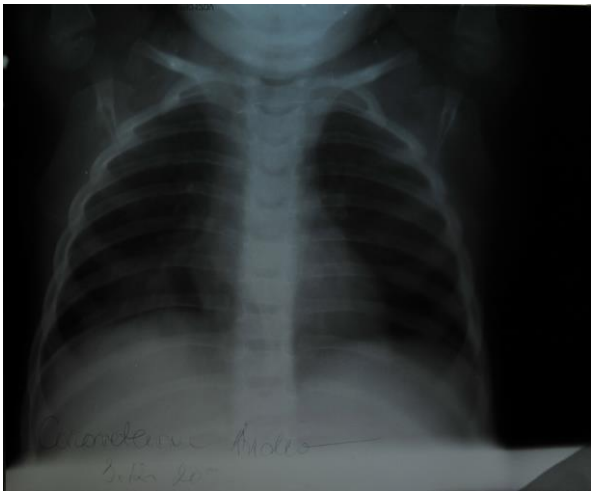

Image 5. Repeated CXR highlighted positive development with marked restriction in intensity and extent of opacity mentioned above.

Discussions

Factors which favor the aspiration of foreign bodies are (3,4):

- age: most cases are found in children between 6 months and 4 years, with a higher frequency between 11 months and two years of age,
- increased curiosity of children regarding the surrounding environment developed by a maximum exploratory activity between hand and mouth (5),
- the tendency of children to run or play during feeding,
- the absence of molars decreases the ability to chew food sufficiently, leaving large chunks of non-chewed food,
- young children have a decreased ability to chew and an increased respiratory rate, so any object placed in the mouth has a higher possibility of being aspired than in older children (6),
- children do not have a complete coordination of the mouth and tongue,
- small children lack the coordination between swallowing and glottis closure.

Foreign bodies are classified by origin: exogenous and endogenous; by structure: organic and inorganic (2,7). Organic foreign bodies: peanuts, bread, vegetables, and irritants: beans, corn, walnut, popcorn, seeds, pumpkin skin, sunflower, watermelon and other fruits, bones, meat. There are authors who claim that organic substances are most commonly aspirated (7,8). We did not find in the medical literature a case like this in which the patient aspired grass inflorescence, as it happened in our case (8).

Organic foreign bodies are usually radiologically invisible and cause early infectious accidents, being difficult to extract because they crumble at the extraction (9). The organic foreign bodies tend to swell due to local moisture, to cause stenosis, destructions and cause large reactions (10).

In this case, bronchoscopy failed to reveal the grass inflorescence and the repeated radiological examination revealed no special parts, but the general condition of the patient, the antalgic position, respiratory failure, pulmonary stetacustic, biological samples (leukocytosis= 407,000/mm^3, neutrophilia**,** ESR increased over 100 mm), anamnestic context drew attention. In this case, the aspiration of the grass inflorescence occurred in the context of a respiratory infectious episode.

The right pneumothorax installed on the 6th day of hospitalization was produced by the perforation of the pleura. Most foreign bodies stop in the right bronchus because the diameter of the main bronchus is bigger than the left one, the divergence point from the tracheal axis is smaller in the right (the bronchus is more vertical), the air flow through the right lung is bigger than the left lung one (11,12). In our case the location of the foreign body was on the right side, too.

For the treatment of this case, a multidisciplinary medical team was involved, consisting of specialists in

pediatrics, pediatric surgery, pediatric otolaryngology, radiology.

As a feature of this case, we consider its evolution: from the moment of aspiration – noticed by the parents – to the first admission when she presented poor general condition, fever, right antalgic position, respiratory failure, subcrepitant rales in the right lung area; radiological tests and the bronchoscopy did not reveal the foreign body when the right sided pneumothorax appeared. It followed a six months slack, after which she removed the grass inflorescence in a coughing fit, followed by hemoptysis, when the x-ray examination showed the condensation aspect on the right lung area and later the emphasis of bronchiectasis at the level of a right side terminal bronchus.

A pulmonary CT would have helped to highlight the foreign body. The grass inflorescence produced lesions in the lung parenchyma and, when eliminated, lesions at the bronchi level with hemorrhagic manifestations. The removal of the grass inflorescence by the child revealed the foreign body and led to healing.

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The manuscript must be in English, typed single space, one column on A4 paper, with margins: top – 3 cm, bottom – 2,26 cm, left – 1,5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author's correspondence address.